The Journal

of the

Louisiana State Medical Society

$4.00 Per Annum, 35c Per Copy
Vol. 108, No. 10

OCTOBER, 1956

Published Monthly
1430 Tulane Avenue, New Orleans 12, La.

THE ARTERY BANK AND ARTERIAL GRAFTS
PART II. ARTERIAL GRAFTING *

REICHARD KAHLE, M. D. †
NEW ORLEANS

Since arterial grafting involves the question of an artery bank as well as consideration of the problems associated with use of the grafts themselves, it was believed desirable to consider the subject in two parts. The first part, which discussed artery banks and methods of collection and storage, appeared in a previous issue of the Journal.[1] A basic knowledge of the physiology, function and fate of such grafts is obviously pertinent to this discussion. These, together with the indications, results and future of arterial grafting will be considered in the second part. Case summaries will be used to illustrate some of these points.

INTRODUCTION

Gross, Bill and Peirce[2] initiated the modern era of arterial grafting in 1949, when they reported use of homologous arterial grafts in 15 human beings. In view of the pioneering efforts of Alexis Carrel[3-6] in this field early in the present century, it is surprising that clinical use of arterial grafts had not developed more rapidly prior to 1949. The reason for the delay was neither lack of technical knowledge nor failure to appreciate the vast surgical possibilities that arterial grafting presents, because Carrel possessed both knowledge of the technical fundamentals and a vivid and prophetic imagination as to their possible uses. Had modern mehods of anesthesia for thoracic surgery and antibiotic and chemotherapeutic drugs been available earlier, undoubtedly the story of arterial grafting would have been different.

TYPES OF GRAFTS

Three kinds of vascular grafts are used: autogenous, homologous and heterologous. An autogenous graft is one taken from one part of an individual's body to be used in another part. A homologous graft is one taken from another animal of the same species. A heterologous graft is one in which the donor is an animal of a different species. Also, vascular grafts may be arterial or venous, or they may be fabricated of a foreign substance, such as a plastic (nylon, dacron or orlon). Finally, experimental evidence indicates that under certain circumstances it may be possible to induce a host to develop his own endothelial lined tube which could be used as a graft.[7]

FUNCTION AND FATE OF ARTERIAL GRAFTS

In regard to arterial grafts two questions almost invariably are asked. The first is whether or not a living graft is necessary and the other concerns its ultimate fate.

Viability—In the early days of renewed interest in arterial grafting, a living graft

---

* Presented at the Seventy-sixth Annual Meeting of the Louisiana State Medical Society, Alexandria, La., May 23-25, 1956.

† From the Department of Surgery, Tulane University School of Medicine, New Orleans.

This work was supported in part by the Louisiana Heart Association through Grant C-552, and in part by the Edw. G. Schlieder Foundation through Grant C-393.

was believed to be desirable, if not a necessity. Gross and associates [2,8] devoted much time and thought to development of a proper nutrient medium. By using a modified Tyrode's solution, they found that viable cells could be cultured from the graft as long as thirty-five to forty days after storage. Gradually, however, it became apparent that a living graft was not necessary. Indeed, results of some experimental studies seem to indicate that a dead graft may be less likely to become thrombosed than a living one damaged by collection and storage.[9] It has been shown, for instance, that platelets and intima possess similar electrical charges. With injury, the electrical charge of the endothelial cells of the intima may be reversed. Rather than repelling each other, then, the intimal cells and platelets having opposite charges would attract and might initiate development of a thrombus.

The low incidence of thrombosis in larger homologous grafts is perhaps surprising but even more amazing is the persistence of patency in grafts made from foreign materials, such as nylon, orlon, or dacron. The tremendous rate of flow through larger vessels undoubtedly plays a part in keeping the vessel open, since the incidence of thrombosis is much higher in vessels smaller than the aorta and iliacs. The fact that the new vessel rapidly becomes lined with a smooth endothelial-like substance also helps to prevent occlusive thrombosis. In a matter of hours the inner surface of a homologous graft or of a plastic prosthesis, such as orlon, placed in contact with the moving blood stream, becomes covered with a smooth fibrin-like substance that serves eventually as a scaffold for the growth of new intimal cells.

Intimal cells grow from the ends of the host vessels to form a new lining for adjacent portions of the graft. In longer grafts, however, the intima of the central portion is not derived from this source but rather from the ingrowth of endothelial cells through the wall of the homograft or the interstices of the plastic cloth.

Fate—Much of the fundamental investigation on the fate of homografts has been done by Hufnagel and Eastcott [10] and Deterling and associates.[11-13] As might be expected from Carrel's original description, the graft acts as a scaffold for the ingrowth of new fibrous tissue. In approximately six months the smooth muscle and elastic fibers are replaced by fibrous connective tissue. In view of this it is not surprising that after a period of time grafts lose much of their elasticity. This fact should not be used to condemn their use, since in the majority of instances, they perform their function well and are usually far superior, even with the passage of time, to the patient's own diseased vessels. The chances of the graft outliving the patient are excellent, since life expectancy in the age group in which a graft is commonly indicated probably is considerably reduced.

The case of C. S., a white man 59 years old, illustrates this point. He had a thrombosed aortic bifurcation (Leriche's syndrome), which was replaced by a homologous arterial graft at Ochsner Foundation Hospital, on June 14, 1955. Pulsations in the pedal vessels were restored and remained good throughout the remainder of the patient's life. He died on Feb. 12, 1956, as a result of extensive plasma cell myeloma. At autopsy the graft, which had been inserted eight months previously, was grossly normal and resembled a normal aortic bifurcation. The intima of the aorta and of both iliacs was smooth and glistening, and the vessels were widely patent (Figure 1). On microscopic examination the walls showed the expected fibrosis but the functional utility was perfect.

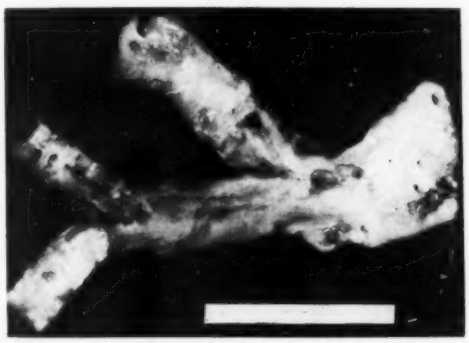

Figure 1.—(Case C. S.): Luminal surface of aortic graft nine months after insertion. Note smooth intimal lining.

Since arterial grafts have been in extensive use in human beings for less than

seven years, no one knows their ultimate fate fifteen to twenty years following grafting. Dilatation and calcification may occur but this need not be a deterrent to use of this life saving measure. The possibility of dilatation and the tendency to thrombosis can be greatly reduced by proper matching of the diameters of the host vessel and the graft, care being taken to avoid constriction at the suture line or dilatation at any point. The importance of this has been stressed by Schmitz and associates.[14] The lucid explanation by Holman [15] of the hemodynamic factors causing dilatation distal to a stenotic area in the vascular system is also pertinent to this problem.

INDICATIONS AND RESULTS

Aneurysms—The rising incidence of arteriosclerotic aneurysms due to increased life expectancy is probably more than compensating for the decreasing incidence of syphilitic aneurysms, which has resulted from the extensive use of penicillin early in the disease. Management of aneurysms is therefore more than an academic problem. Furthermore, the prognosis of these lesions, if untreated, is extremely poor. Kampmeir,[16] for instance, reported that only 18 of 633 patients with syphilitic thoracic aneurysms were alive two years after initial symptoms.

The brilliant work of DeBakey and colleagues [17-21] in the resection and replacement of abdominal and thoracic aneurysms has brought new hope to patients with these lesions. In a recent publication they [17] reported an extremely low mortality rate and gratifying results in the surgical treatment of 35 patients with thoracic and 101 with abdominal aneurysms.

Our more limited experience with these lesions bears out the encouraging results that can be obtained in their treatment by grafting For example:

L. D., aged 50 years, came to the Ochsner Clinic in April 1954 for treatment of midabdominal pain, which had been present for a number of years and was becoming progressively worse. Examination showed an expansile pulsation in the area of the aortic bifurcation which measured approximately 9 by 7 by 5 cm. The aneurysm was resected on April 30, 1954, and the diseased aorta was replaced by a bifurcation graft. The patient has resumed driving his taxicab and has had no impairment of circulation in the lower extremities since the operation.

If it is at all possible, the patient's artery should be used to restore continuity. In the case of aneurysms this can only occasionally be done. However, this is particularly important if the vessel is medium sized, since the incidence of thrombosis in grafts of smaller vessels is appreciable and since it may be expected to be increased if the graft must traverse a flexion crease of an extremity.

An interesting case of popliteal aneurysm that illustrates both employment of the patient's vessel and the value of a graft is that of

J. M., a Negro man 64 years old, who was admitted to Charity Hospital in New Orleans March 14, 1956, with bilateral popliteal aneurysms. The one on the right measured approximately 13 by 12 by 5 cm. and the necrotic skin over the apex gave warning of imminent rupture. At operation, on the night of admission, the aneurysm on the right was resected. This left a gap of only about 4 cm. between the ends of the popliteal artery but the ends could be approximated without too much tension by partial flexion of the knee. It was decided to do this rather than place a graft in the medium sized artery. Circulation in the leg was excellent. The patient's leg was extended beginning on the twelfth postoperative day. Convalescence seemed uneventful but on the thirty-third postoperative day there was profuse hemorrhage from the right popliteal area. It was assumed that the suture line had given away because of tension, but at exploration the source of hemorrhage was found to be the popliteal artery about 3 cm. above the suture line, which was intact. There was a blow-out resembling a mycotic aneurysm (Figure 2). Presumably, this was due to rupture of the arterial wall from the clamp that had been used in the original operation. Review of the record also suggests that infection was present even at the time. The ruptured artery was resected and the defect was bridged by a femoral artery homograft measuring 4 cm. Circulation in the leg was excellent.

Resection of aneurysms of the thoracic aorta and replacement with arterial homografts is a relatively new step in the definitive treatment of this condition. Unlike the case in coarctation, collateral circulation in thoracic aortic aneurysms is not well developed. For this reason, provision must be made for maintenance of blood supply to the spinal cord while the aorta is cross

Figure 2.—(Case J. M.): Mycotic aneurysm of popliteal artery. A 4 cm. segment of the artery was resected and replaced by a homologous graft.

clamped to perform the anastomosis. A temporary shunt may be used, as suggested by Schafer and Hardin.[22] We have employed this method in the laboratory and on one patient but use of hypothermia, as suggested by Cooley and DeBakey,[23] seems simpler and technically safer in most instances in which the period of occlusion need not be too extensive.

The latter method was used in the case of Mr. G. C., aged 53 years, who complained chiefly of intense pain in the epigastrium boring through to the back. Aneurysmal dilatation of the thoracic aorta with erosion of the bodies of the eighth and ninth thoracic vertebrae was demonstrated roentgenographically. The result of the serologic test for syphilis was positive. On May 14, 1956, the patient was operated on at Baptist Hospital. Body temperature was reduced to approximately 86° F. by packing in ice. An incision was made through the bed of the eighth rib and a segment of the descending aorta measuring approximately 12 cm. in length and containing the aneurysmal sac, which measured about 10 by 8 by 5 cm., was removed. The cavity in the vertebral bodies that formed the lining of the sac posteriorly was packed with gelfoam. Recovery was uneventful except for a transient rise in the nonprotein nitrogen level. The patient's blood nitrogen level prior to operation had been elevated and operation had to be delayed until this tendency to uremia ‡ had been controlled. When last seen about two months postoperatively, the patient was relieved of the boring epigastric pain and circulation in the lower extremities was normal.

‡ Medical management by Dr. Kenneth G. Nix.

Vascular Obstruction—In addition to aneurysms, obstruction of the larger and medium sized vessels due to arteriosclerosis may, in many instances, be best treated by arterial grafting. Thrombosing aortic bifurcation, for instance, is best treated by resection of the abdominal aorta and replacement with a graft.[24] In instances of segmental obstruction in the smaller arteries, such as the femoral, however, use of a by-pass shunt without resection of the obstructed segment and resultant destruction of collaterals is attracting ever increasing attention.[25]

Several cases are cited to illustrate a number of points that are relevant to this phase of the subject. The first is an example of patency of a bifuraction graft for over two years with relief of symptoms of ischemia of the lower extremities due to arteriosclerotic obstructive disease.

Mrs. L. C., a white woman 51 years old, suffered from cold feet, claudication and weakness of the muscles of the lower extremities which prevented her from working. On May 14, 1954, at Ochsner Foundation Hospital the aortic bifurcation and both common iliacs were replaced with a homograft. She is able to walk without claudication, both feet are warm, her exercise tolerance is greatly increased, and she has returned to work.

The next case illustrates use of a double bifurcation graft to relieve ischemic symptoms of the lower extremities resulting from arteriosclerotic thrombotic disease. Prior to operation, Mr. G. C. a white man 55 years old, was forced to stop walking after taking only 100 steps because of cramping in the thigh and calf muscles. In May 1956, at Baptist Hospital, the abdominal aorta, was resected just below the inferior mesenteric artery and anastomoses were made to both external and both internal iliac branches. Pulsations to both dorsalis pedis and both posterior tibial arteries returned immediately and improvement in function has been dramatic. The patient now has no exercise "ceiling." Although not always feasible, use of a graft to restore flow to the internal iliacs as well as the external, as was accomplished in this case, is worth doing when possible.

The recent case of Mr. A. H., a white man 46 years old, illustrates the extent of resection that is sometimes necessary. He was operated on at Charity Hospital in New Orleans, on June 29, 1956. Bilaterally, the external iliac arteries were obstructed to just above Poupart's ligament at

the level of origin of the deep epigastric vessels. Proximally, when the aorta was divided just below the renal vessels, no flow was obtained. It was necessary to remove a plug of soft thrombus from the artery to obtain a normal flow. A bifurcation homograft approximately 20 cm. in length was used to replace these obstructed vessels from just below the renal arteries to the common femoral artery. Anastomoses were carried out to both external iliacs and to the internal iliac on the right, where it was necessary to perform thrombo-endarterectomy to get back flow.

Coarctation—Use of grafts to replace the resected segment of coarctation of the aorta which is so extensive that the remaining ends cannot be reapproximated by suture has been described by Gross.[8] A graft may also be necessary even if the coarctation is short if the patient is past the third decade of life, since the aorta near the coartation is often friable in these older patients and this might make suturing the vessel end to end technically difficult or impossible.

The case of Mr. E. B. illustrates this point. A diagnosis of coarctation was made at the age of 32 years, when, in search for a cause of his headaches, his physician noted that his blood pressure was 180 mm. Hg. systolic and 100 mm. Hg. diastolic in the upper extremities and 110 mg. Hg. systolic and 70 mm. Hg. diastolic in the lower. At Charity Hospital in New Orleans, on March 25, 1954, the coarctation was resected. To bridge the resulting defect it was necessary to use a graft 8 cm. long. The patient has resumed his occupation as a truck driver. His blood pressure is now 140 mm. Hg. systolic and 95 mm. Hg. diastolic in the left arm and 150 mm. Hg. systolic and 100 mm. Hg. diastolic in the right. Careful observation during the two years since operation has shown no evidence of dilatation or calcification in the graft.

Cancer Surgery — Arterial grafts may play an important role in the progress of the surgical treatment of cancer. If, for instance, the factor that precludes completion of an otherwise satisfactory radical neck dissection is carcinomatous involvement of the common or internal carotid artery, the vessel may be sacrificed and replaced by a graft. Expeditiously done, the graft will prevent the occurrence of cerebral damage and possibly death secondary to loss of a carotid.

Injury—Extensive arterial trauma is not uncommon even in the civilian population. If the laceration of the arterial wall is clean and incisive with no ragged or traumatized edges, or if the gap in the vessel is not too great after resection of the traumatized arterial section, the method of choice is primary repair without a graft. This is true, even if the injury has not been recently sustained. Obviously, insertion of a graft in repairing an artery that is unquestionably expendable is meddlesome surgery. This implies, of course, knowledge of the arteries that may or may not be sacrificed. The experiences of Jahnke and associates [26-29] in the Korean War have served to emphasize this fact. In 34 cases of major vascular injuries treated by primary repair or vein graft, amputation was necessary in only 3.

Only recently has use of an arterial graft in the treatment of an arteriovenous aneurysm received attention, since often the continuity of the artery can be restored by the transvenous route, as emphasized by Matas.[30] Furthermore, the extensive collaterals that develop in time usually permit ligation of the main arterial trunk should repair not be feasible. The value of grafts in arteriovenous fistulas has been emphasized by Seeley and associates' [31] experience with Korean casualities. The following case illustrates the fact that occasionally an arterial homograft may be of service in the management of arteriovenous communications in civilian life.

R. R., a 14 year old boy, accidentally injured his left brachial vessels on Dec. 5, 1955, when a linoleum knife slipped and penetrated his forearm just below the bend of the elbow. Apparently the injury to the vessels was overlooked by the intern who gave him emergency treatment. He was referred § two months after injury because of a rapidly enlarging, pulsating swelling in the left forearm. The radial pulse on this side was barely palpable, and obliteration of the pulsation in the mass by pressure caused the hand to turn cold, pale, and bluish. It was believed that the extremity distal to the vessels would be viable if ligation were done but that the blood supply would be greatly diminished and that growth might be disturbed if continuity were not restored. The rapid enlargement of the aneurysm made delay undesirable. The continuous thrill and murmur over the mass, the prominence of the superficial

§ By Dr. F. C. Boyce.

veins, and the warmth of the digits in the absence of a radial pulse gave evidence of the arteriovenous nature of the aneurysm. Branham's sign was elicited, the heart rate slowing six beats per minute on obliteration of the mass.

At operation on February 16, 1956, at Hotel Dieu it was found that transvenous reconstruction of the artery was technically impossible. Instead, a triangular patch of arterial homograft was inserted in the anteromedial surface of the brachial artery just above its bifurcation where a defect had resulted from the wound (Figure 3). The

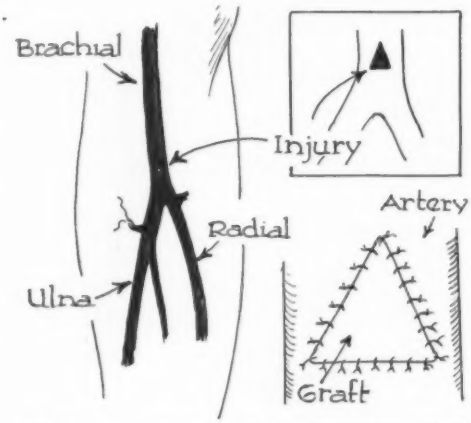

Figure 3.—(Case R. R.): Traumatic arteriovenous aneurysm of left brachial vessels. Defect in artery repaired by "patch" graft.

continuity of the artery was thereby maintained without constriction of its lumen, which undoubtedly would have occurred had the edges of the rent been approximated without the graft. Full radial pulsation returned immediately and has remained during the ensuing months. Function is normal.

TECHNIC

The necessity for careful ligation or suture of branches of the graft was emphasized in the section dealing with preparation of the graft. As in suture of all vessels, the adventitia is stripped from the vessel near the ends to be sutured. This avoids "dragging" of the suture and puckering of the edges of the vessel. Furthermore, adventitial tags, dragged into the lumen, could conceivably be the focal point for the origin of thrombosis.

Although there are theoretic advantages to an everting suture placing intima to intima, this classic vascular suture technic is not always used. More often, in the interest of time and facility, the simple over suture is used. This technic has withstood the test of time and is the one most popular, at least for aortic anastomosis.

Space does not permit a detailed description of the special instruments used in vascular surgery. Noncrushing clamps of various sizes, shapes, and designs are necessary as well as a knowledge of when and how to use them. Bulldog clamps designed on the principle of the Potts clamp are invaluable for working on the iliacs and other vessels in the pelvis.

THE FUTURE OF ARTERIAL GRAFTING

Plastic Grafts—Alexis Carrel long ago experimented with use of mechanical prostheses, such as paraffin lined glass and and aluminum tubes, to replace the aorta in in animals. The modern era, however, of the use of plastic substances to replace resected vessels may be said to have begun in 1952, with the report of Voorhees, Jaretski and Blakemore,[32] who described use of tubes of a plastic cloth known as Vinyon-N to replace the aorta in experimental animals. Since then, numerous reports on use of plastic "blood vessels" have appeared in the literature but the search for the ideal substance has not ended. In the laboratory of the Department of Surgery at the Tulane University School of Medicine we have experimented with vinyon-N, orlon, dacron, and nylon. From any of these substances a suitable vessel may be made but they offer certain disadvantages.

In order to serve satisfactorily these plastics must meet certain requirements. Obviously, they must be inert and must be non-wetting in order to discourage clotting. They must also be woven in such a way that leakage through the mesh is not excessive. Initially, in most of these plastics there is a tendency to exude blood but with the proper material this stops after a minute or two and a satisfactory channel results (Figure 4).

One of the most vexing problems has been the question of branching. Obviously, a bifurcation graft can be sewed as needed but this involves not only inconvenience but also the necessity of more luminal irregularity as a result of a longer and more

Figure 4.—Orlon tube used to replace abdominal aorta in experimental animal sacrificed at three weeks. Lumen patent and "intimal" surface smooth.

complex seam. The problem can be met by properly woven or knitted seamless grafts and considerable progress has been made in this direction.[33, 34] Textile manufacturers in general, however, have been reluctant to become involved, understandably, because the outlay for equipment is great, the financial return is negligible and most important, they could conceivably become involved in law suits in spite of the most humane of motives.

Unquestionably, "grafts" of plastic cloth lack normal elasticity. What the ultimate result of this might be is unknown but it is probably not important if used to replace relatively short vascular segments in older patients.

Like arterial homografts, they serve as scaffolds on which new tissue may grow. They become lined with intima in the same way and fibroblasts grow into the meshes of the material to form thickened, relatively normal appearing vessels. When animals in which we had replaced the abdominal aorta six months or more previously were killed, patent functioning vessels were found in a high percentage.

A problem presented by plastic grafts which is not of the same magnitude in homografts is that of development of kinking, compression and thrombosis in the area where these artificial vessels cross a flexion crease. The normal resiliency of homografts makes them more suitable if this contingency must be faced. Edwards,[35] however, has made an ingenious attempt to solve this problem. If the nylon "grafts" are crimped on a mold, the desired change in direction may be made without collapse of the tube. This is the same principle as that employed in the rubber hose of the ordinary anesthetic apparatus. Edwards [36] has also recently advocated use of these crimped tubes in replacement of peripheral arteries and believes that the stretch and pliability of these tubes permit success in these medium sized vessels in which straight tubes failed.

Although this is far too great an oversimplification of the matter of plastic replacement, the subject might be summarized by saying that in the absence of an adequate homograft, plastic grafts can be used in human beings, the incidence of thrombosis in the larger vessels is low but in medium sized vessels such as the femoral it is approximately 50 per cent, and the future with new plastics and new methods of manufacture of branching seamless arterial prostheses is promising.

Heterologous Grafts—Carrel's successful use of heterologous grafts in two exper-

imental animals would seem to have indicated long ago that the future might be bright for use of animal vessels to replace human ones. The abattoir would provide an obvious plentiful supply if this were true. Furthermore, Hufnagel [37] recently reported results of experimental studies that suggest the suitability of heterologous grafts and on this basis he used them in 4 human beings. On the other hand, experimental work by Creech and coworkers [38] indicated that they are not suitable. Heterologous grafts, however, have an important use as temporary shunts to carry sufficient circulation while extensive resection of the arch of the aorta and descending aorta is being carried out.[39, 40]

SUMMARY

At present the artery bank is the only means by which the availability of a suitable arterial graft can be assured. Grafts may be collected under sterile or asterile technic. Although delay is not desirable, as much as eight hours may elapse between death of the donor and collection of the graft. In regard to the age of the donor, the decision should be based solely on the physiologic rather than the chronologic, age of the artery. Patients who have died of a transmissible or malignant disease are not considered suitable donors of an arterial graft. Grafts may be stored by the quick frozen or freeze drying method.

Types of grafts include autogenous, homologous, and heterologous arterial or venous grafts, and plastic grafts. There is experimental evidence to suggest that under certain circumstances it may be possible to induce a host to develop his own endothelial lined tube which could be used as a graft. Use of a living graft is not necessary. Homologous grafts and plastic prostheses both serve as a scaffold for the ingrowth of fibroblasts which convert the structure into a less elastic but functionally satisfactory tube. A new intima is developed which is grossly indistinguishable from the normal.

Indications for arterial grafting include aneurysms of the abdominal or thoracic aorta, localized arteriosclerotic obstruction of the abdominal aorta as well as of the peripheral arteries, extension of radical cancer excision and repair of arteriovenous aneurysms. Illustrative case histories are included.

The future of plastic arterial prostheses is promising but the ultimate decision as to the best material and the long term fate of these "grafts" is not settled. Heterologous grafts probably should not be used.

REFERENCES

1. Kahle, Reichard: The artery bank and arterial grafting. Part I. The artery bank, J. Louisiana State M. Soc. 108:271, (August), 1956.

2. Gross, R. E., Bill, A. H., Jr. and Peirce, E. C., III: Methods for preservation and transplantation of arterial grafts, Surg., Gynec. & Obst. 88:689, 1949.

3. Carrel, Alexis: La technique operatoire des anastomoses vasculaires et la transplantation des visceres, Lyon med. 98:859, 1902.

4. Carrel, Alexis and Guthrie, C. C.: Uniterminal and biterminal venous transplantation, Surg., Gynec. & Obst. 2:266, 1906.

5. Carrel, Alexis: On the experimental surgery of the thoracic aorta and the heart, Ann. Surg. 52:83, 1910.

6. Carrel, A.: Ultimate results of aortic transplantation, J. Exper. Med. 15:389, 1912.

7. Fisher, B., Rosencrans, D., Adams, C. and Fisher, E. R.: The fate of autogenous skin tubes as aorta grafts, Surg., Gynec. & Obst. 102:309, 1956.

8. Gross, R. E.: Treatment of certain aortic coarctations by homologous grafts; a report of nineteen cases, Ann. Surg. 134:753, 1951.

9. Sawyer, P. N. and Pate, G. W.: A study of electrical potential differences across the normal aorta and aortic grafts of dogs; research report, Naval Medical Research Institute, National Naval Medical Center, Bethesda, Md., 1953.

10. Hufnagel, C. A. and Eastcott, H. G.: Homologous arterial grafts, Bull. Georgetown Univ. M. Center 4:119, 1951.

11. Deterling, R. A., Jr., Coleman, C. C., Jr. and Parshley, M. S.: Experimental studies of the frozen homologous aortic graft, Surgery 29:419, 1951.

12. Coleman, C. C., Jr., Deterling, R. A., Jr. and Parshley, M. S.: Some long-term observations on aortic homografts, Surgery 37:64, 1955.

13. Deterling, R. A., Jr.: Discussion of DeBakey et al. See reference 17.

14. Schmitz, E. J. and others: The influence of diameter disproportion and of length on the incidence of complications in autogenous venous grafts in the abdominal aorta, Surgery 33:190, 1953.

15. Holman, Emile: The development of arterial aneurysms, Surg., Gynec. & Obst. 100:599, 1955.

16. Kampmeier, R. H.: Saccular aneurysms of the thoracis aorta; Ann. Int. Med. 12:624, 1938.

17. DeBakey, M. E., Cooley, D. A. and Creech, O: Aneurysms and occlusive diseases of the aorta; analysis of 203 cases treated by resection and homograft replacement. Henry Ford Hospital International Symposium on Cardiovascular Surgery, Philadelphia, W. B, Saunders Co., 1955, p. 468.

18. Cooley, D. A. and DeBakey, M. E.: Surgical considerations of intrathoracic aneurysms of the aorta and great vessels, Ann. Surg. 135:660, 1952.

19. Cooley, D. A. and DeBakey, M. E.: Surgical con-

siderations of excisional therapy for aortic aneurysms, Surgery 34:1005, 1953.

20. DeBakey, M. E. and Cooley, D. A.: Successful resection of aneurysm of thoracic aorta and replacement by graft, J. A. M. A. 152:673, 1953.

21. DeBakey, M. E. and Cooley, D. A.: Surgical treatment of aneurysm of abdominal aorta by resection and restoration of continuity with homograft, Surg., Gynec. & Obst. 97:257, 1953.

22. Schafer, P. W. and Hardin, C. A.: The use of temporary polyethylene shunts to permit occlusion, resection and frozen homologous graft replacement of vital vessel segments, Surgery 31:186, 1952.

23. Cooley, D. A. and DeBakey, M. E.: Resection of the thoracic aorta with replacement by homograft for aneurysms and constrictive lesions, J. Thoracic Surg. 29:66, 1955.

24. Linton, R. R. and Menendez, C. V.: Arterial homografts; a comparison of the results with end-to-end and end-to-side vascular anastomoses, Ann. Surg. 142:568, 1955.

25. Crawford, E. S. and DeBakey, M. E.: The by-pass operation in the treatment of arteriosclerotic occlusive disease of the lower extremities, Surg., Gynec. & Obst. 101:529, 1955.

26. Jahnke, E. J., Jr. and Seeley, S. F.: Acute vascular injuries in the Korean War; an analysis of 77 consecutive cases, Ann. Surg. 138:158, 1953.

27. Jahnke, E. J., Jr. and Howard, J. M.: Primary repair of major arterial injuries; report of fifty-eight battle casualties, A. M. A. Arch. Surg. 66:646, 1953.

28. Hughes, C. W.: The primary repair of wounds of major arteries, Ann. Surg. 141:297, 1955.

29. Cooke, F. N., Hughes, C. W., Jahnke, E. J., Jr. and Seeley, S. F.: Homologous arterial grafts and autogenous vein grafts used to bridge large arterial defects in man, Surgery 33:183, 1953.

30. Matas, R.: Surgery of the vascular system, Chapt. LXX in Keen's Surgery 5:303, 1920.

31. Seeley, S. F., Hughes, C. W., Cooke, F. H. and Elkin, D.: Traumatic arteriovenous fistulas and aneurysms in war wounded, Am. J. Surg. 83:471, 1952.

32. Voorhees, C. B., Jr., Jaretski, A., III and Blakemore, A. H.: The use of tubes constructed of vinyon "N" cloth in bridging arterial defects, Ann Surg. 135:332, 1952.

33. Sanger, P. W., Taylor F. N., McCall, R .E., Duchesne, R. and Lepage, G.: Seamless synthetic arterial grafts, J. A. M. A. 160:1403, 1956.

34. Sanger, P. W., Taylor, F. H., Matsuba, Takuro and Salomone, Frank: The use of artificial fiber as an artery substitute, Ann. Surg. 143:862, 1956.

35. Edwards, S. W. and Tapp, J. S.: Chemically treated nylon tubes as arterial grafts, Surgery 38:61; 89, 1955.

36. Edwards, W. S.: Peripheral artery replacement with chemically treated nylon tubes, Surg., Gynec. & Obst. 102:443, 1956.

37. Hufnagel, C. A., Rabil, P. J. and Reed, L.: A method for the preservation of arterial homo- and heterografts, Surgical Forum (1953), Philadelphia, W. B. Saunders, 4:162, 1954.

38. Creech, O., Jr., DeBakey, M. E., Self, M. and Halpert, B.: The fate of heterologous arterial grafts; an experimental study, Surgery 36:431, 1954.

39. Chamberlain, M. J., Klopstock, R., Parnassa, P., Grant, A. R. and Cincotti, J. J.: The use of shunts in surgery of the thoracic aorta. J. Thoracic Surg. 31:251, 1956.

40. Stranahan, A., Alley, R. D., Sewell, W. H. and Kausel, H. W.: Aortic arch resection and grafting for aneurysm employing one external shunt. J. Thoracic Surg. 29:54, 1955.

—————o—————

THE MALABSORPTION SYNDROME *

MARTIN S. KLECKNER, JR., M. D. †
NEW HAVEN, CONN.

The malabsorption syndrome, the sprue syndrome and jejuno-iliac insufficiency comprise a synonymous group of conditions characterized by impaired absorption of fat, carbohydrate, protein, vitamins, iron and calcium in the small intestine. As a consequence, malnutrition, steatorrhea, loss of weight, anemias, tetany and avitaminosis are predominant clinical manifestations.

Much of our current knowledge on the absorption of food is derived from a report of Munk [1] published in 1891. He made a series of observations on a young woman with a filarial chylous fistula, in much the same way as William Beaumont did on the stomach of Alexis St. Martin. Among several primitive fat-labeling experiments, he conclusively demonstrated that virtually all the fat which is absorbed enters the body by the lymphatic route. Since then it has been concluded that fatty acids of 10-carbon atoms or less are probably absorbed by the portal route; whereas the longer chain fatty acids, which make up the bulk of the dietary fatty acids, are absorbed by the lymphatic route.

The particular defect in the malabsorption syndrome appears to be fairly specific and cannot be explained on the basis of one single mechanism. It has been demonstrated experimentally in normal human beings that amino acids, glucose and fat compete in intestinal selective absorption.[2] These substances, in addition to essential minerals, vitamins, particularly the fat soluble vitamins A, D, and K, and water, are defectively or poorly absorbed by the intestines in patients with this syndrome.

For a discussion of the pathogenesis of the malabsorption syndrome the reader is referred to the recent thorough review of

---

* Presented at the Seventy-sixth Annual Meeting of the Louisiana State Medical Society, Alexandria, La., April 24, 1956.

From the Section on Gastroenterology, Ochsner Clinic and Department of Medicine, Tulane University of Louisiana School of Medicine, New Orleans.

† Now Assistant Professor of Medicine, Yale University School of Medicine, New Haven, Conn.

the literature by Paterson.[3] He listed the current opinions of the postulated defect in this condition as: intermediary metabolic disorder, intrinsic cellular defect, dietary or vitamin deficiency, motor dysfunction of the small intestine, and altered colonic bacterial flora. Actually, the basic etiology of sprue, for example, is unknown and the prevailing concept is that it is a deficiency caused by defective intestinal absorption due to an inborn error of metabolism.

CLASSIFICATION

A clinical classification of the malabsorption syndrome lacks both etiologic and pathologic relationships (Table 1). In

TABLE 1
CLASSIFICATION OF MALABSORPTION SYNDROME

- A. Primary sprue
  - 1. Celiac disease
  - 2. Nontropical sprue
    - a. Gluten-induced enteropathy
  - 3. Tropical sprue
- B. Pancreatogenous steatorrhea
  - 1. Cystic fibrosis of pancreas
  - 2. Chronic relapsing pancreatitis
  - 3. Carcinoma of pancreas
  - 4. Post-pancreatectomy
  - 5. Kwashiorkor
- C. Hepatobiliary steatorrhea
  - 1. Primary biliary cirrhosis
  - 2. Obstruction of common bile duct
- D. Intestinal steatorrhea
  - 1. Anastomotic syndrome
    - a. Resection of small intestine or stomach
    - b. Fistula: gastrojejunocolic fistula
  - 2. Diseases of small and large intestine
    - a. Benign and malignant neoplasms
    - b. Granulomatous disease: regional enteritis
    - c. Infiltrative disease: primary amyloidosis; scleroderma
    - d. Infections: tuberculosis
    - e. Stricture
    - f. Congenital: malrotation of gut
    - g. Antibiotic enterocolitis
  - 3. Diseases of mesenteric lymph nodes: Intestinal lipodystrophy; sarcoma
  - 4. Parasitic infestation; filariasis; diphyllobothrium latum
  - 5. Endocrinopathy; thyrotoxicosis; Addison's disease
  - 6. Pellagra

1940, Bennett and Hardwick, and later others, recognized a sprue-like condition in surgical short-circuiting of the small intestine, internal intestinal fistulas and intestinal lymphoma, among other diseases, and concluded that jejuno-iliac insufficiency, could be corrected surgically.

Occasional cases of nontropical sprue and most cases of celiac disease (Gee-Herter's disease) have been shown to be due to the presence of wheat gluten in the diet. As a result, a satisfactory therapeutic response has been noted only after a gluten-free dietary regimen. Many patients with nontropical sprue have had celiac disease in childhood. The predominant clinical differences between tropical and nontropical sprue, in addition to the geographic location, are, in the former, greater incidence in adults, generally refractory to a gluten-free diet but favorably responsive to oral or parenteral administration of folic acid, and occurrence in epidemic outbreaks or among members of the same family. The main areas in which tropical sprue is epidemic are the Far East, India, and the Caribbean region, but there are local differences in these areas, as for example, its occurrence in Puerto Rico but not in Jamaica. Steatorrhea persists even after the patient moves to a temperate climate. Some patients may show no response to administration of folic acid but recuperate dramatically when intestinal antibacterial therapy is instituted.

Pancreatogenous steatorrhea is associated with those conditions in which there is a deficiency of one or more of the pancreatic enzymes (Figure 1). Increased bacterial growth and fermentation occur, particularly in the colon as the result of undigested food. In our experience it has been one of the most common types of steatorrhea.

Hepatobiliary steatorrhea is a clinical manifestation of obstruction of the common bile duct due to such lesions as stones, stricture, or neoplasm and primary biliary (cholangiolitic) cirrhosis with or without xanthomatosis (Figure 2). Impaired absorption of fat and even protein occurs when bile is excluded from the intestinal tract. Bile salts are considered to be a most important biliary absorptive constituent.

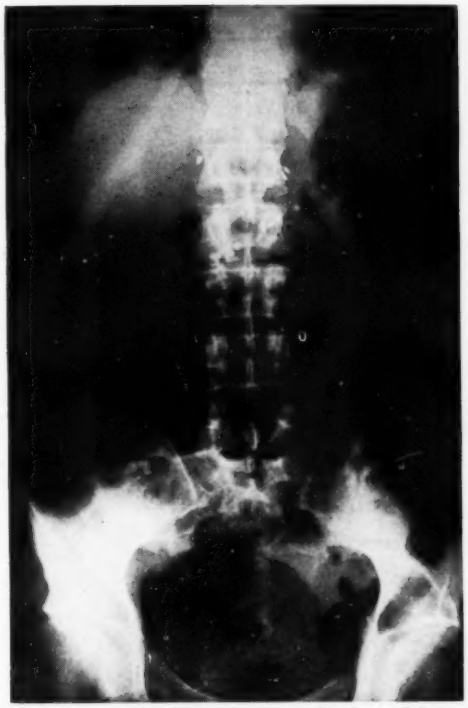

Figure 1—Roentgenogram of the abdomen. Chronic relapsing pancreatitis. Calcification of the pancreas. Pancreatogenous steatorrhea.

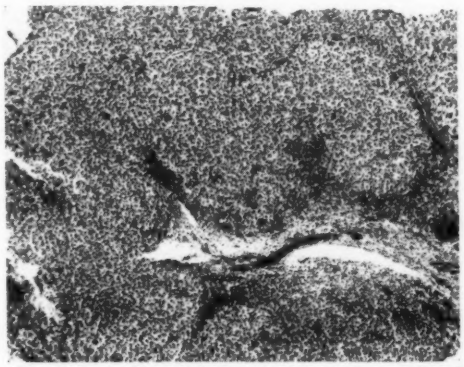

Figure 2—Hepatobiliary steatorrhea. Needle biopsy of the liver. Primary biliary cirrhosis with xanthomatosis. Chronic pericholangitis, bile stasis, and early nodular regeneration (H & E, X 60).

There are various types of intestinal steatorrhea. In most of them gross pathologic changes in the intestinal wall, short-circuiting of the intestinal contents or interference with lacteal transport of fat can be demonstrated. In this category the most prevalent problem of steatorrhea occurs in the patient with the anastomotic syndrome. Postgastrectomy steatorrhea, gastrojejunocolic or gastrocolic fistulas, and inadvertent surgical error of gastroileostomy are representative. In addition to the abnormal routing of chyme in these cases, it is possible that the steatorrhea may be related to the increased amount of intestinal coliform flora as seen in gastrojejunocolic fistula. Significant steatorrhea is seen rarely in the unusual case of "irritable bowel" and in advanced cases of thyrotoxicosis, diabetes mellitus, panhypopituitarism or adrenal insufficiency. Impairment of the lacteal transport of fat in patients with intestinal lipodystrophy (Whipple's disease), lymphoma, metastatic neoplasm and tuberculosis is another type of malabsorption syndrome. Severe pellagra, in patients whose diets consist exclusively of pork, molasses and corn bread, may simulate nontropical sprue.

CLINICAL MANIFESTATIONS

It is commonly believed that celiac disease[5] and nontropical sprue[6,7] represent different stages of the same disease. Both are characterized by chronic diarrhea without a demonstrable or significant pathologic or bacteriologic basis. Additional manifestations are emaciation, flatulence, intolerance to dietary carbohydrate and fat, and an abnormally great requirement for protein in the diet. Progressive malnutrition, steatorrhea, hypoproteinemia and hydrolability occur with the development of mineral and vitamin deficiencies and a negative nitrogen balance (Fig. 3a.).

Celiac disease is seen chiefly in children, although in some, symptoms have persisted into adulthood. Also, the disease may be latent in adolescence and symptomatic in adult life.[8] Not only are spontaneous remissions and relapses characteristic of sprue, but the disease may be latent. In the later instance there is no direct or initial evidence of intestinal malabsorption, but diarrhea, avitaminosis, megaloblastic anemia and spontaneous fractures may be the initial clinical features. The possibility of subclinical sprue should be considered in patients with refractory megaloblastic anemia, particularly younger individuals.

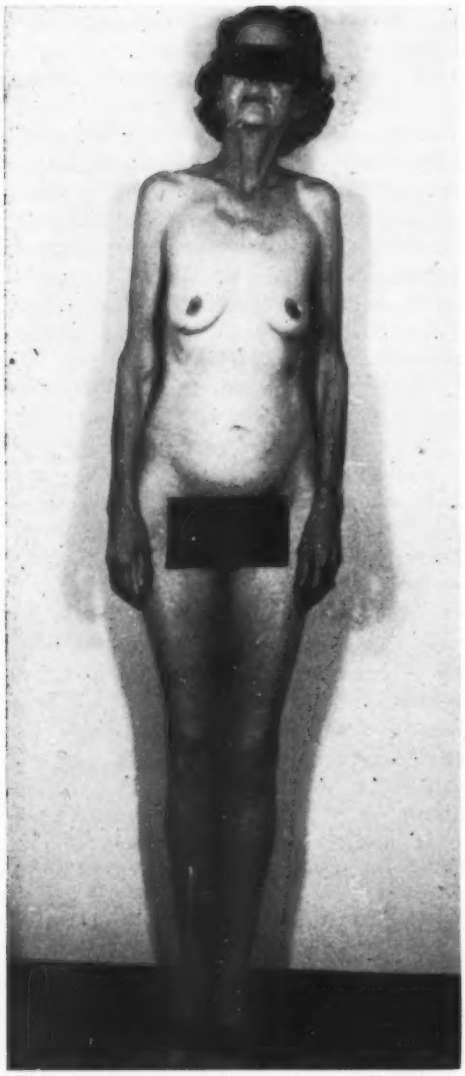

Figure 3a—Nontropical sprue. Emaciation, cutaneous melanosis, dry "toadskin".

Figure 3b—Same patient six weeks later having been on a therapeutic regimen consisting of a high protein, moderate carbohydrate, low fat diet, multivitamins, and a daily maintenance dose of 5 mg. U.S.P. prednisone twice daily.

Nocturnal diuresis, abdominal distention, edema of the ankles, low blood pressure, cutaneous pigmentation, clubbing of the fingers and koilonychia may be present. The alert, apprehensive or hypermetabolic appearance of patients with nontropical sprue is impressive. Many of them give the appearance of a "bird-perched-on-a-limb ready for flight" with their thin pointed noses and staring facial expressions as they sit unrelaxed ready for alarm.

Excessive steatorrhea leads to emaciation and loss of calcium and fat soluble vitamins. Creatorrhea, the fecal loss of protein, appears responsible also for emaciation, fatty liver, osteoporosis, hypoproteinemia, edema, hydrothorax, and ascites. Defective absorption of carbohydrates results in fermentation of the stool, dyspepsia, flatulence, bloating, and hypoglycemia. Almost all patients with the malabsorption syndrome, especially sprue, exhibit polyvalent vitamin deficiencies. Loss of vitamin A may cause night blindness, xerophthalmia, bronchitis and a roughened dry skin. Avitaminosis B may result in glossitis, cheilitis, blepharitis, nasolabial se-

borrhea, peripheral neuritis, diarrhea, pellagrous dermatitis and hypochromic anemia. Loss of vitamin C manifests itself by scurvy and slow healing of wounds. Rickets or osteomalacia is the result of avitaminosis D. Hypoprothrombinemia may develop as the consequence of loss of the fat soluble K in the stool, causing gastrointestinal hemorrhage. In severe cases there may be loss of calcium and phosphorus as well as tetany and osteomalacia.

Clinical manifestations of decreased blood and tissue calcium are noted in the physical signs of tetany: carpopedal spasm, Trousseau's sign, positive Chvostek's sign and muscular cramps. The failure of hypocalcemic tetany to occur in some cases of the malabsorption syndrome may be explained on the basis that as the serum protein concentration decreases so does the proportion of protein-bound calcium, leaving a higher, relative amount of ionized calcium. The skeletal manifestations of hypocalcemia and avitaminosis D include osteomalacia (Figure 4), rickets, dwarfism, lenticular opacities, spontaneous fractures and severe kyphosis.

Figure 4—Roentgenogram of the thoracic spine. Nontropical sprue. Marked osseous demineralization. Osteomalacia. Kyphosis.

Anemia is invariably present during some stage of the malabsorption syndrome. The loss of iron produces hypochromic, microcytic anemia early in the active phase of the disease. This may be aggravated by deficiency of vitamin B complex, hypothrombinemia due to deficiency of vitamin K, and decrease in the amount of stored vitamin C. In the later, quiescent phase, hyperchromic, macrocytic anemia results from defective absorption or excessive loss of folic acid or vitamin B_{12}. The absorption of iron may be impaired also by gastric histamine achlorhydria or hypochlorhydria as commonly observed in this syndrome.

LABORATORY FEATURES

We employ a steatorrhea-creatorrhea test diet in the study of patients having the malabsorption syndrome.[9] This consists of a daily diet composed of 101.6 Gm. of fat, 117.5 Gm. of protein, 269.6 Gm. of carbohydrate, and 2463 calories for five days. At the beginning of the third day and seventy-two hours later a carmine marker is ingested to mark the stool collection. The feces of normal persons in twenty-four hours contains: total solids, 13.6 to 39.1 Gm.; total fat, 1.8 to 6.7 Gm.; and total nitrogen 0.8 to 2.5 Gm. Following resection of 75 per cent of the small intestine for recurrent regional enteritis one patient had 60.4 Gm. of fecal fat and 8.7 Gm of fecal nitrogen in twenty-four hours while on the steatorrhea-creatorrhea test diet. A patient with nontropical sprue had a quantitative fecal fat excretion of 7.7 Gm. and fecal nitrogen excretion of 2.8 Gm. in twenty-four hours.

A flat oral glucose-tolerance curve is obtained in most cases of advanced primary sprue. This is most probably due to an absorptive deficiency, but because there may be a normal glucose tolerance curve in these cases when glucose is administered via duodenal tube, a gastric defect can be postulated.

We employ the intravenous secretin test

for the quantitative determination of pancreatic enzymes. By use of a Diamond tube introduced into the first portion of the duodenum under fluoroscopic guidance, the volume of the secretion and amounts of bicarbonate, trypsin, amylase and lipase are determined in three consecutive twenty minute collections after the cautious intravenous administration of one unit of secretin per kilogram of body weight. In pancreatic steatorrhea these substances are absent or present in small amounts; whereas normal amounts occur in other types of steatorrhea. Congenital fibrocystic disease of the pancreas may be differentiated more practically from celiac disease by the oily appearance of the stool, the presence of neutral fat rather than calcium soaps in the stool, a high glucose tolerance curve and association of parenchymal pulmonary cystic fibrosis.

Elevation of the basal metabolic rate, volvulus of the colon,[10] low serum carotene levels, flat oral vitamin A tolerance curve, low cholesterol and plasma lipid levels, and gastroscopic evidence of atrophic gastritis are additional laboratory observations in cases of the malabsorption syndrome.

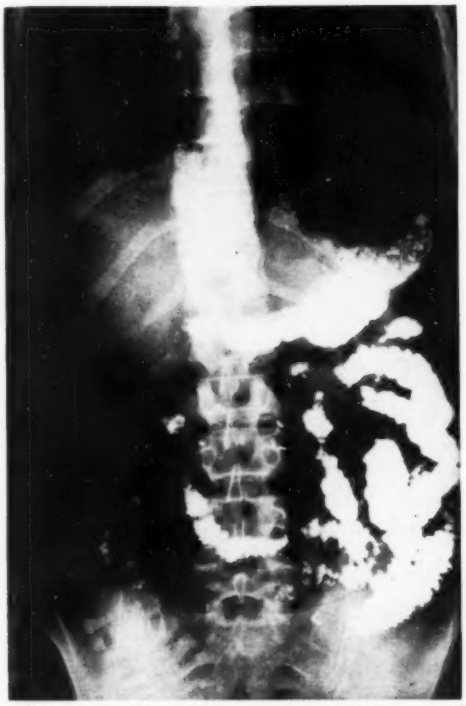

Figure 5—Two hour roentgenogram of the small intestine in nontropical sprue. Moulage, segmentation, dilatation, and a feathery appearance.

ROENTGENOLOGIC FEATURES

Roentgenologic evidences of intestinal malabsorption include obliteration of the valvulae conniventes (Kerkring's folds) with smooth margins of barium-filled small intestine; sausage-like smooth, dilated, barium-filled loops of small intestine —the "moulage sign"; adherence of barium to the mucosa of the intestine after the bulk of this substance has passed the area giving it a feathery, fleck-like, flocculent appearance; dilatation of the involved loops of intestine; hypomotility of the intestine particularly with stasis and hypersecretion in the gastric and ileal areas; secondary megacolon, and finally, evidence of osteomalacia and osteoporosis (Figures 4, 5). A normal small intestinal pattern is seen infrequently in sprue and commonly in other types of the malabsorption syndrome. The "sprue pattern" is sufficiently characteristic radiologically to separate it from the heterogeneous group of conditions hitherto labeled as "deficiency pattern" or disordered motor function.[11] Even after proper therapy this pattern persists in patients with primary sprue.

TREATMENT

Treatment of the malabsorption syndrome depends upon the causative factor of the particular case. If the cause is intestinal stricture, enteric fistula, short-circuiting of the small intestine, extrahepatic biliary obstruction, pancreatic fistula, congenital malrotation of the intestine, regional enteritis, operable neoplasm, or surgical error, the treatment of choice would be surgical as determined by each individual case. Steatorrhea secondary to parasitic infestation and various metabolic diseases, as thyrotoxicosis, adrenal insufficiency, panhypopituitarism and diabetes mellitus, may resolve when the primary disease is treated specifically.

There are, however, certain general measures which may be employed in the management of patient's with the malab-

sorption syndrome. We use a "foundation diet" consisting of 2130 calories, composed of 45 Gm. of fat, 135 Gm. of protein and 300 Gm. of carbohydrate. During a symptomatic remission, or when additional caloric intake is required, a "full diet" may be employed in the amounts of 75 Gm. of fat, 140 Gm. of protein and 330 Gm. of carbohydrate making a total of 2540 calories.[12] Because of the excessive loss of calcium, 4 to 12 Gm. of calcium glucinate or lactate is administered by mouth in daily divided doses. Vitamins afford particular value, especially those that are fat soluble. These are administered conveniently in the amounts contained in the standard therapeutic multivitamins together with at least 5 mg. of vitamin K daily. Synthetic aqueous vitamin A in large doses is preferable to the fat soluble type.

Certain specific therapeutic measures are employed, particularly in patients with primary sprue. In pancreatic steatorrhea U.S.P. pancreatin tablets are recommended in a daily oral dosage of at least 10 to 15 Gm. Dilute hydrochloric acid is valueless in the adjunctive management of the malabsorption syndrome. Fat emulsifying agents, as Sorlate (R), may be employed in the dosage of 1.5 Gm. three times daily, but if the effects are unpredictable, oral administration of bile salts in hepatobiliary steatorrhea will produce dramatic reduction in fecal fat, particularly if the oral fat intake is adjusted to a moderately low but palatable level. When intestinal hypermotility or massive intestinal resection is responsible for steatorrhea, anticholinergic drugs may be necessary to impede intestinal hypermotility. We have found JB-340 * (25 mg. four times daily by mouth) to be the most effective available colonic anticholinergic drug.

Celiac disease and late celiac disease (gluten-induced enteropathy) may respond favorably to a wheat-gluten free diet.[3, 13, 14] Wheat and rye gluten are automatically eliminated from the diet of these patients, but it is important to insure that the intake of both calories and protein is necessarily high. As a result of this dietary regimen absorption of fat and nitrogen is increased within a few days and recovery is rapid. In patients with celiac disease this diet should be maintained until the child stops growing.

In tropical sprue administration of a sprue diet and 5 to 25 mg. daily of folic acid orally should be adequate.[15, 16] Symptoms are rapidly relieved, and roentgenologic and other laboratory abnormalities are corrected. If hematologic or neurologic remission is inadequate, crude liver extract, vitamin B_{12} or yeast should be included in the regimen. If this regimen fails to produce remission, removal of the patient to a more temperate climate[17] or institution of intermittent five day courses of an intestinal antibacterial drug is indicated. Any of the broad spectrum antibiotic agents, such as chloramphenicol or tetracyclin, may be administered orally or in various combinations in a dosage of 500 mg. three times daily for five days followed by succinylsulfathiazole in a dosage of 2 Gm. four times daily for five days.

More recently, prolonged administration of adrenocorticotropic hormone,[18] cortisone[19] or hydrocortisone has been demonstrated to induce a remission of nontropical sprue (Table 2). In nontropical sprue, intestinal lipodystrophy (Whipple's disease) and regional enteritis, amelioration of the primary disease, reduction of steatorrhea and improvement in the fat soluble avitaminotic state have resulted in dramatic clinical improvement (Fig. 3b.). Addition of steroid therapy to orally administered ferrous sulfate has corrected otherwise refractory hypochromic, microcytic anemia of the malabsorption syndrome.[20] Presumably, steroids help induce a great increase in the uptake of iron by the intestinal mucosal cells. Although the anemia may respond to administration of iron, iron and cortisone, liver extract, folic acid, vitamin B_{12} or intestinal antibacterial therapy, depending upon the type and phase of the disease, surgical correction of the existing pathologic lesion, for example,

* Kindly supplied by Dr. Harvey S. Sadow, Associate Director of Research, Lakeside Laboratories Inc., Milwaukee, Wisconsin.

TABLE 2
LABORATORY EVIDENCE OF REMISSION IN WOMAN 47 YEARS OLD WITH NON-TROPICAL SPRUE TREATED BY FOUNDATION SPRUE DIET, MULTIVITAMINS AND VITAMINS AND PREDNISONE

	Before	8 Weeks Later
BMR, %	+16	—6
Prothrombin, % of normal	42	100
Serum calcium, mg./100 cc.	3.3	4.7
Serum albumin/ Globulin, Gm./100 cc.	2.4/2.1	3.6/1.5
Stool Guaiac Reaction	positive	negative
Oral Glucose Tolerance Curve	Flat	Low
Serum Vitamin A, microgram/100 cc.	40	70
Histamine Gastric Analysis, Free HC1/ Total HC1, units	0/20	0/14
Stool Fat, Gm./24 hr.	17.2	7.2
Stool Nitrogen, Gm./24 hr.	4.8	1.4
Total Serum Lipids, mg./100 cc.	320	468
Hemogram	hypochromic microcytic anemia	Normal

stricture of the small intestine, will correct the anemia. Normal fecal fat levels are usually obtained in a patient with nontropical sprue receiving steroid therapy. Whereas in my experience the therapeutic results from folic acid, liver extract, or vitamin B_{12} have been nonspecific and erratic in patients with nontropical sprue in the northern part of the United States, my medical associates at Tulane University assure me that folic acid, in particular, has been effective in inducing symptomatic remission in patients in the southern sections of the country. It seems plausible that rather than a direct effect of adrenal hormones in fat absorption, more likely the small intestine shares in the general bodily improvement and that fat absorption improves together with the general restoration of normal metabolic processes in the entire body.

SUMMARY AND CONCLUSION

The malabsorption syndrome, jejunoiliac insufficiency and sprue syndrome comprise a heterogeneous group of diseases in which the intestinal absorption of important foodstuffs, minerals and vitamins is impaired. It is important that primary sprue be differentiated clinically from other types of intestinal steatorrhea and from pancreatogenous and hepatobiliary steatorrhea in order that proper treatment be selected. The recognition that celiac disease, which may be latent in childhood and symptomatic in adulthood, and certain cases of nontropical sprue respond favorably to a gluten-free diet is an important therapeutic advance. The specific use of adrenal steroids in other cases of nontropical sprue and intestinal lipodystrophy, and as adjunctive treatment in regional enteritis has led to effective symptomatic remission, especially in nontropical sprue. Treatment of tropical sprue consists primarily in use of folic acid or administration of antibiotic agents. In fact, recent studies disclosed that the increased coliform flora in both the small and large intestines of patients with the sprue syndrome explain at least in part the defective absorption of necessary food, mineral, and vitamin substances.

Addendum: The patient mentioned in Table 2 experienced a clinical relapse whenever steroid therapy was discontinued. Eventually, a gluten-free diet and therapeutic vitamins (twice daily) were prescribed solely. More marked clinical and biochemical amelioration than during steroid therapy has persisted for seven months.

REFERENCES

1. Munk, J.: Cited in Combined Staff Clinic: Malabsorption syndrome, Am. J. Med. 15:790 (Dec.) 1953.

2. Necheles, H., Sporn, J. and Bridgewater, A.: Absorptive and postabsorptive relationships among foodstuffs, Gastroenterology, 29:993 (Dec.) 1955.

3. Paterson, J. C. S.: The sprue syndrome, Am. J. M. Sc., 231:92 (Jan.) 1956.

4. Bennett, T. I. and Hardwick, C.: Chronic jejunoileal insufficiency; pathogenesis of coeliac disease, tropical sprue, and other conditions, Lancet, 2:381 (Sept. 28) 1940.

5. Anderson, D. H. and di Sant Agnese, P. A.: The celiac syndrome. In Brenneman, Practice of Pediatrics, vol. 1, chap. 29.

6. Friedlander, P. H. and Gorvy, V.: Steatorrhoea, a review of 40 patients, with particular reference to diagnosis, Brit. M. J., 2:809 (Oct. 1) 1955.

7. Frazer, A. C.: Steatorrhoea, Brit. M. J., 2:805 (Oct. 1) 1955.

8. Cooke, W. T., Peeney, A. L. P. and Hawkins, C. F.: Symptoms, signs and diagnostic features of idiopathic steatorrhea, Quart. J. Med., 22:59 (Jan.) 1953.

9. Wollaeger, E. E., Comfort, M. W. and Osterberg, A. E.: Total solids, fat and nitrogen in the feces. III. A study of normal persons taking a test diet containing a moderate amount of fat; comparison with results obtained with normal persons taking a test diet containing a large amount of fat, Gastroenterology, 9:272 (Sept.) 1947.

10. Aldersberg, D. and Schein, J.: Pathology and clinical studies of sprue, J. A. M. A., 134:1459 (Aug. 23) 1947.

11. Aldersberg, D., and others: The roentgenologic appearance of the small intestine in sprue, Gastroenterology, 26:579 (April) 1954).

12. Mayo Clinic Diet Manual, ed. 2, W. B. Saunders Co., Philadelphia, 1954, p. 63-67.

13. Dicke, W. K.: Cited by Paterson.[3]

14. Ross, C. A. and others: Coeliac disease; the relative importance of wheat gluten, Lancet, 1:1087 (May 28) 1955.

15. Berry, L. J. and Spies, T. D.: Present status of folic acid, Blood 1:271 (July) 1946.

16. Weir, J. F. and Comfort, M. W.: Folic acid therapy in nontropical sprue; results of treatment in 7 cases, J. Lab. & Clin. Med., 32:1231 (Oct.) 1947.

17. Stefanini, M.: Clinical features and pathogenesis of tropical sprue, Medicine, 27:379 (Dec.) 1948.

18. Drenick, E. J., Hvoboll, E. and Halsted, J. A.: Effect of ACTH and cortisone on fat absorption of various causes, New England J. Med., 253:303 (Aug. 25) 1955.

19. Taylor, A. B., Wollaeger, E. E., Comfort, M. W. and Power, M. H.: The effect of cortisone on non-tropical sprue (idiopathic steatorrhea), Gastroenterology, 20:203 (Feb.) 1952.

20. Kelley, M. L., Jr., Logan, V. W. and Christ, L. M.: Correction of the anemia of malabsorption syndrome (nontropical sprue?) by oral administration of cortisone and iron, New Eng. J. Med., 252:658 (April 21) 1955.

—o—

THE MECHANISM AND DIFFERENTIAL DIAGNOSIS OF ABNORMAL BLEEDING *

DANIEL W. HAYES, M. D. †
NEW ORLEANS

For many surgeons, bleeding abnormally means that a ligature has come off or a clamp has slipped. Fortunately these mishaps can usually be remedied without much difficulty. On the other hand, hemorrhage in a patient who has had no surgery is potentially a difficult problem with myriad possible solutions. As an internist interested in hematology and allied fields, I shall present a medical discussion of the fascinating problem of the inability of blood to clot with a plan of attack in meeting such an obstacle.

* Presented at the 8th Annual Meeting of the Surgical Assn. of Louisiana, November 6, 1955, New Orleans.

† Section of Internal Medicine, Mahorner Clinic. Clinical Instructor in Medicine, Louisiana State University School of Medicine.

The history is probably the most important means to determine whether the bleeding is caused by some local pathology such as ulcer, neoplasm, or infection or whether it is due to an abnormal vascular or coagulation mechanism. Almost never does a patient have massive or severe bleeding as the first manifestation of a generalized disease. Questioning will elucidate the fact that there has been easy bleeding or bruising in the past following minor trauma or occurring spontaneously. Every surgeon of any type or specialty can avoid serious misfortune by getting this past history.

VASCULAR ABNORMALITIES

Injury to large blood vessels of course causes hemorrhage (Table 1) and no more need be said about this except that the obvious treatment is to ligate or clamp the leaking vessels.

TABLE 1
CAUSES OF HEMORRHAGE

A.	Injury to large blood vessels.
B.	Vascular dysfunction.
	1. Hereditary telangiectasia.
	2. Senile purpura.
	3. Hypertension, diabetes, infections.
	4. Nonthrombocytopenic purpuras.
	a. Allergic purpura.
	b. Henoch's or Schoenlein's purpura.
	5. Scurvy.

Vascular dysfunction may include several different types of abnormalties. Hereditary telangiectasia occurs in both sexes and is a hereditary condition which consists of local angiomata, which have a deficient muscular and elastic layer. This condition is often absent in childhood and is not seen until later in life. These telangiectatic blood vessels occur in the skin where they are most often recognized but it is from the mucous membrane angiomata that the large hemorrhages occur in this condition.

Purpura or gross bleeding with large ecchymotic areas or hematomas under the skin occurs in older people merely from fragility of the blood vessels, usually the veins, with loss of supporting structure in the surrounding tissues. Characteristically this occurs only in the elderly patient.

Two obvious causes of hemorrhage include hypertension with its increased pres-

sure in the blood vessels leading to easy bleeding, and diabetes which seems to have some definite effect on weakening blood vessel walls. Infectious diseases are prone to cause hemorrhage either by direct weakening of the capillaries or by depressing the platelet count.

Purpuras that have normal platelet counts, that is, non-thrombocytopenic purpuras, are often seen. The allergic type of purpura usually occurs in association with allergies and may occur with other skin manifestations or allergies such as erythema, wheals, bullae and other obviously allergic rashes.[1]

Henoch's purpura has been described as occurring mainly in children and adolescents. Usually gastrointestinal symptoms are present and colic often occurs. The bowel is edematous and red in segmental distribution. Joint symptoms may also occur in rare association with the gastrointestinal systems. Schoenlein's purpura is described as occurring in young adults and usually occurs as periarticular effusions. These may also be manifestations of an allergic disease.

Scurvy is vitamin C deficiency and occurs because there is a deficiency in the ground substance between the cells of the capillary walls with increased capillary fragility.

COAGULATION MECHANISM

Most of the remainder of this discussion will present the complicated and fascinating aspects of the coagulation of blood.[2, 7] The bare details (Figure 1) of the coagulation mechanism show in phase one, that tissue cells or platelets break down to liberate the platelet thromboplastic factor which is also named thromboplastinogenase. This platelet thromboplastic factor combines in some way with a plasma thromboplastic factor which is always present in the plasma, also called thromboplastinogen or antihemophilic globulin. In the presence of a plasma thromboplastic component and a plasma thromboplastic antecedent these substances form thromboplastin.

In the second phase, thromboplastin, calcium ions, and certain prothrombin conversion factors facilitate the formation of thrombin from prothrombin. The thrombin thus formed also acts to labilize platelets so that more platelets are broken down. The thrombin also acts to increase the

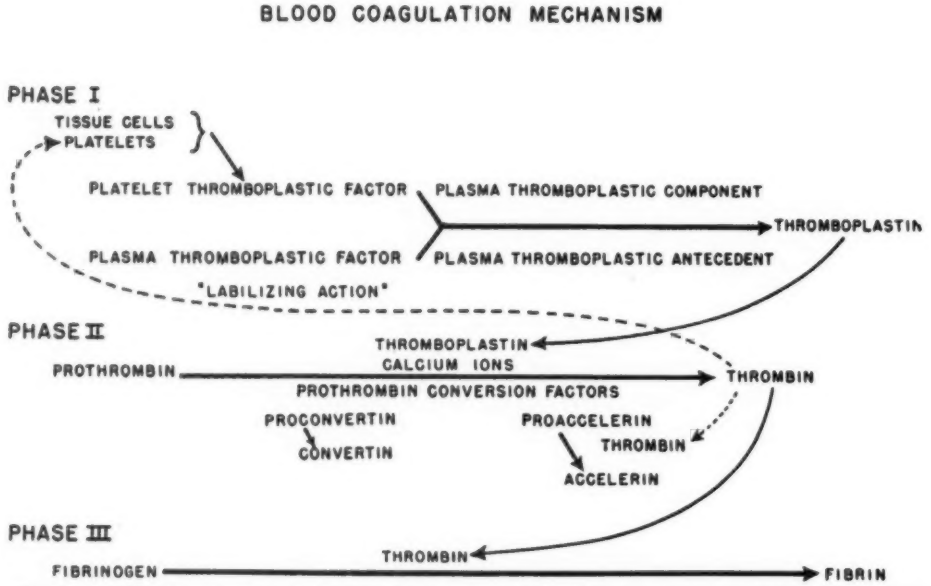

Figure 1. The blood coagulation mechanism. An abbreviated composite of the three phases of blood coagulation.

amounts of accelerating factors so that the speed of this reaction then becomes greatly quickened. With adequate amounts of thrombin thus formed fibrinogen is polymerized and formed into fibrin clot.

COAGULATION - PHASE 1

Let us discuss in detail the first phase of blood coagulation and then discuss various coagulation defects which may be found in the first phase. (Figure 2)

The platelets agglutinate and then lyse or become destroyed. The exact mechanism of this lysis is not entirely known and while it is precipitated by the contact of the platelets with a rough capillary wall yet there may be other factors which cause this disintegration of the platelet. As was previously stated the break-down of platelets is much accelerated by the formation of minute amounts of thrombin at the site of the blood clot formation. Thrombin may be always in the blood, inactivated by antithrombin. This platelet thromboplastic factor thus formed combines with a plasma thromboplastic factor which is otherwise called antihemophilic globulin or active thromboplastinogen. Quick[5] feels that thromboplastinogen must be activated before it can combine with the platelet thromboplastic factor, and that there is a certain circulating anticoagulant which may inhibit this activation of thromboplastinogen so that the disease acts like hemophilia but actually is not hemophilia. The plasma thromboplastic component which has recently been discovered is also a necessary element in this combination of the previous two factors to make thromboplastin. A plasma thromboplastic antecedent also has recently been described.

CLINICAL SYNDROMES - PHASE 1

We shall now consider in detail the various coagulation defects that occur in this first phase of blood coagulation with a few brief clinical remarks about each one. (Table 2) Platelet deficiency occurs in the well known idiopathic thrombocytopenic purpura. A circulating antiplatelet factor occurs in many patients and is thought to agglutinate the patient's own platelets as well as repeatedly transfused platelets. Hypersplenism has also been implicated, but fewer hematologists now support this theory of sequestration and destruction from hypersplenic activity alone. The disease may be acute and self-limited, particularly in children, and it often occurs after an upper respiratory illness in some. In chronic or recurrent thrombocytopenia bleeding will occur frequently. The spleen is usually small and not palpable. If the spleen is very large it is probably secondary throm-

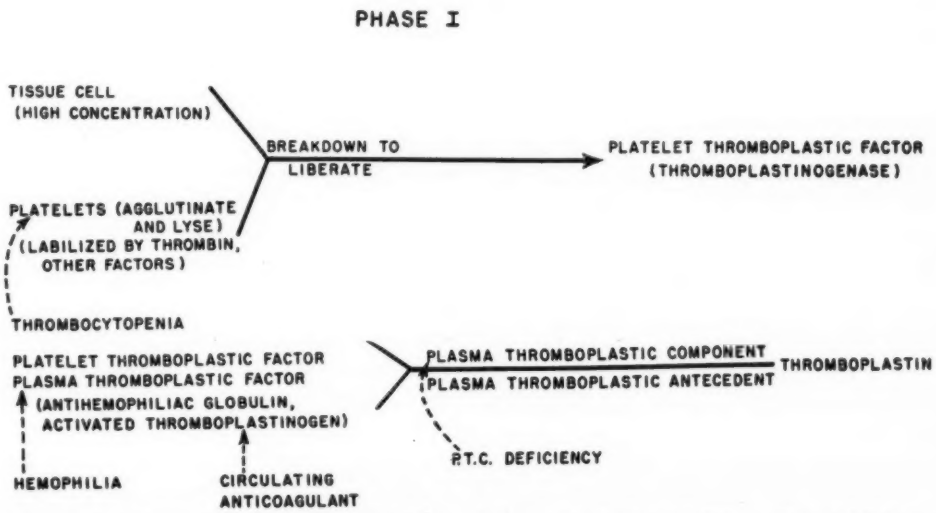

Figure 2. Phase I. Detailed presentation of steps involved. Conditions that inhibit or retard reactions are indicated by dotted arrows below the reaction.

TABLE 2
COAGULATION DEFECTS

- **A. Phase I.**
  - 1. Platelet deficiency
    - a. Primary thrombocytopenic purpura
    - b. Secondary thrombocytopenic purpura
    - c. Thombasthenia
  - 2. Plasma factor defects
    - a. Plasma thromboplastic factor (hemophilia)
    - b. Plasma thromboplastic component
    - c. Plasma thromboplastic antecedent
- **B. Phase II.**
  - 1. Prothrombin deficiency
    - a. Vitamin K deficiency
    - b. Liver disease
    - c. Anticoagulants
    - d. Congenital
  - 2. Calcium deficiency
  - 3. Prothrombin conversion factor deficiences
    - a. Proaccelerin to accelerin (AC globulin or labile factor)
    - b. Proconvertin to convertin (SPCA or stable factor)
- **C. Phase III**
  - 1. Afibrinogenemia
  - 2. Fibrinogenopenia
  - 3. Fibrinolysins

bocytopenia and not a primary thrombocytopenia. In the bone marrow the megakaryocytes are increased in idiopathic type of thrombocytopenia whereas in the secondary type the megakaryocytes may be decreased or absent. The use of ACTH or cortisone may cause remission of this condition, especially in children when it often shortens the course of the self-limited disease. Splenectomy is indicated in a recurrence or relapse or if the bleeding is uncontrollable. Splenectomy should be done if possible during a remission since it may be dangerous during the acute phase. In 75 per cent of patients a cure may be expected.[10]

Secondary thrombocytopenia may be divided into three categories. First, splenomegaly due to lymphomas, Banti's syndrome, acute or chronic infections, infectious mononucleosis, and sarcoidosis. In the second place decreased megakaryocytes in the bone marrow may occur as a result of chemical damage, and physical agents such as x-ray. It may also occur in aplastic anemia of various causes or in leukemia. Treatment of secondary thrombocytopenia involves treating the underlying disease. A third possibility is a syndrome which is called thrombotic thrombocytopenic purpura in which platelet thrombi occur in many areas of the body giving neurologic signs, signs of purpura plus a hemolytic anemia. This condition is a rare one but is seen often enough that one should keep it in mind in the differential diagnosis. This is similar to the Schwartzmann phenomenon seen in animals in anaphylactic shock.

Thrombasthenia, also called pseudohemophilia, falls into an ill-defined group between hemophilia and thrombocytopenic purpura. Some of these conditions are due to abnormal platelets even though the platelet counts are within normal limits; yet the bleeding time may be prolonged, there may be delayed prothrombin consumption or prolonged clot retraction. The addition of normal platelets may correct the abnormal laboratory tests. A qualitative defect in the platelets is probably present in these cases. Some cases which previously have been placed into this classification now may be described as plasma thromboplastic component (P.T.C.) deficiencies.

Plasma factor defects include the defect known as hemophilia. Hemophilia is a sex-linked recessive characteristic. In a recent publication ten men gave their ideas in a classic symposium on "What is Hemophilia".[9] Each man had a different idea as to what hemophilia was and there was not too much agreement as to the boundaries of the definition of hemophilia. Final proof rests on the fact that the unknown plasma fails to correct the plasma defect in a known hemophiliac. Classical hemophilia is described as an absence of antihemophilic globulin. The latter may also occur as a result of pregnancy, repeated transfusions or other generalized diseases. Deficiency of prothrombin conversion factors may also be a factor in hemophilia-like conditions.

Treatment of the hemophiliac involves prevention as well as therapy of hemorrhage. Some advise regular and frequent plasma infusions to prevent bleeding des-

pite the obvious and severe hazard of serum hepatitis. Infusions of fraction I of the plasma are said to produce antibodies and resistance to therapy more rapidly than citrated whole or fresh frozen plasma. ACTH may alter this resistance: Fraction I is not as potent as it was once said to be. This is probably because of changes induced in the processing.

During hemorrhage or surgery plasma or fresh blood should be used daily or more often if needed to maintain normal clotting until wounds are healed. Locally, the liberal use of bovine topical thrombin and pressure to bleeding lesions is important provided debris and clotted blood are first removed. Refrigerated thrombin should be kept in the patient's own home.

PTC component deficiency is also known as Christmas disease because it was first described in a patient by that name. This condition can vary from mild to severe. It is sex-linked, recessive, and appears mostly in men. Clinically it appears like hemophilia, but chemically it is different. It varies from normal coagulation and normal prothrombin consumption time to a coagulation time longer than eight hours, but antihemophilic globulin (or fraction I) does not cure these cases. It is corrected by blood, plasma, or serum and local thrombin, as well as plasma thromboplastic component administration. This PTC is in serum and plasma but antihemophilic globulin is only in plasma.

PTA (antecedent) deficiency is corrected by blood or plasma or serum. It causes slight prolongation of the coagulation time and the prothrombin consumption test.

COAGULATION - PHASE 2

We shall now discuss in more detail the second phase of the blood coagulation. (Figure 3) Prothrombin is changed to thrombin in the presence of thromboplastin, calcium ions and certain prothrombin conversion factors. Inhibitors of the reaction and of the various factors concerned in the equation are indicated by the dotted lines below the equation. Vitamin K is a necessary precursor to the formation of prothrombin which is always present in the circulating blood. Prothrombin can probably form minute amounts of thrombin initially as a slow part of this reaction; then the thrombin acts to facilitate the production of accelerin or serum AC globulin from its inactive precursor, the labile factor or plasma AC globulin or proaccelerin as we see it here. This reaction is the main accelerator of the prothrombin reaction and proaccelerin is found only in the plasma. The stable factor or convertin or SPCA is formed from

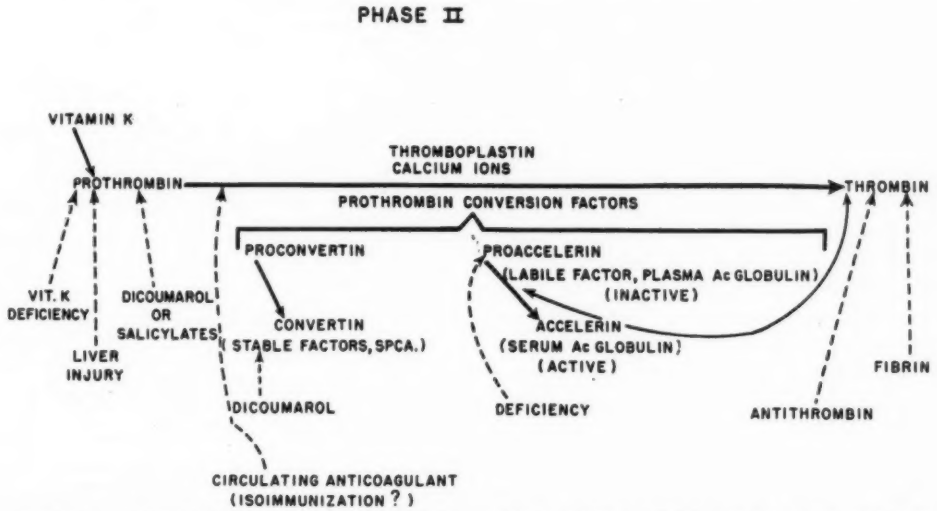

Figure 3. Phase II. The conversion of prothrombin to thrombin with details of other factors concerned in this phase. Inhibitors are indicated by dotted arrows.

proconvertin and it also accelerates the reaction but it is not used up in the reaction. This is the factor that is decreased markedly by dicumarol but is present in both plasma and serum. It is increased in amount in pregnancy which may help to explain the high incidence of thrombo-embolism. The conversion factors again, let me say, affect the speed of the reaction markedly but have little effect on the actual formation of thrombin.

CLINICAL SYNDROMES - PHASE 2

Obviously if there is a deficiency in vitamin K there will be a deficiency in prothrombin. (Table 2) This can occur from a deficient diet which is rare in mammals; it can occur when there is no bile entering the intestine to facilitate the absorption of vitamin K, as in obstructive jaundice or biliary fistula. It can occur in the newborn and is known as hemolytic disease of the newborn. There is a decrease in the biosynthesis of vitamin K_1 in the sterile intestinal tract as well as a low serum prothrombin conversion accelerator (or the stable factor). In liver disease the prothrombin cannot be formed from the vitamin K. Transfusion of blood, plasma or vitamin K_1 as well as improvement in liver function will correct this deficiency.

Anticoagulants such as salicylates and dicumarol form another factor in prothrombin deficiency. Dicumarol acts in some way on the liver to reduce the prothrombin content, as well as by decreasing the proconvertin content. The treatment of dicumarol or salicylate-induced hypoprothrombinemia is the administration of blood, plasma or vitamin K_1 in doses of 50 to 150 mgm. intravenously. Heparin is also an anticoagulant, the exact site or mode of action of which has not yet been determined. It probably acts as an antithrombin as well as to adversely interfere with the thrombin-fibrinogen interaction. Hyperheparinemia is treated with intravenous protamine sulfate, 100 or 200 mgm. or toluidine blue 300 to 400 mgm. daily. These combine as basic compounds with heparin, a strongly acid substance, to form insoluble and inactive salts.

There are also certain congenital deficiencies of prothrombin due to factor or factors unknown.

Calcium deficiency usually is not a factor in the coagulation defects since calcium deficiency which is severe enough to cause changes in the coagulation of blood usually is incompatible with life since the patient has long since died of hypocalcemic tetany.[8]

Prothrombin conversion factor deficiencies have been known as parahemophilia in previous studies. This is now felt to be a deficiency in AC globulin. The deficiency of labile factor or plasma AC globulin is corrected by fresh blood or fresh plasma transfusions. The addition of thromboplastin does not return coagulation to normal as it does in hemophilia. The labile factor, as would be presumed by its name, disappears in stored blood and often a shift from bank blood to fresh blood is lifesaving when massive transfusions have to be used which almost replace the total blood volume, since then an acquired AC globulin deficiency would be produced in the course of treatment. Deficiencies in the stable factor also known as proconvertin, convertin or SPCA can be treated by plasma, blood, serum or even vitamin K_1.

COAGULATION - PHASE 3

We will now discuss the third phase of blood coagulation, (Figure 4) the formation of the fibrin clot from fibrinogen in the presence of thrombin. Fibrinogen is always present in the circulating blood and if thrombin is formed it will cause fibrin to be polymerized from fibrinogen. Heparin is an antithrombin which tends to slow the interaction of the thrombin on fibrinogen and so will slow the clot formation. This is one of the factors in the anticoagulant activity of heparin, the other being its prevention of the action of thromboplastin to influence the prothrombin conversion to thrombin.

CLINICAL SYNDROMES - PHASE 3

The coagulation defects (Table 2) in phase three include decreased or absent amounts of fibrinogen in the plasma. These are rare conditions but do occur often enough to be considered. Afibrinogenemia renders the blood completely incoagulable

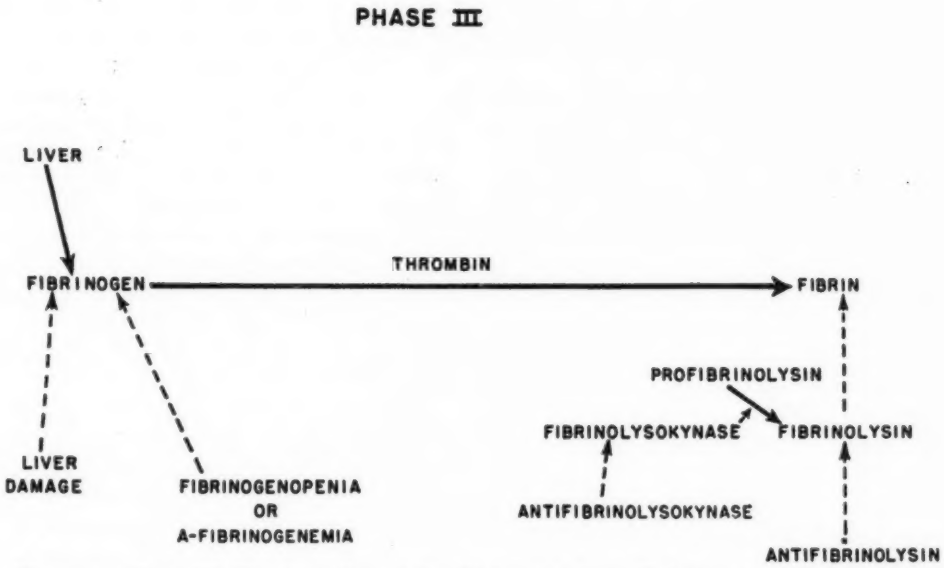

Figure 4. Phase III. The formation of the fibrin clot from fibrinogen in the presence of thrombin. A diagrammatic scheme of the fibrinolysin activity to dissolve clots is also presented.

even with added thrombin. Fibrinogenopenia can occur as a congenital defect.

Acquired fibrinogenopenia may occur as a complication of liver disease. More recently other conditions have been described in which hypofibrinogenemia may occur. As an occurrence with certain complications of pregnancy it should be detected. Premature separation of the placenta, amniotic fluid embolism, severe pre-eclampsia or eclampsia, or presence of a dead intrauterine fetus could also occur at or near parturition as a cause of excess bleeding from fibrinogenopenia.[6]

Shock, or neoplastic disease of the prostate, pancreas or stomach may also be a factor. Pulmonary surgery with manipulation of the lungs has been described as a cause of hypofibrinogenemia. It is often associated with increased fibrinolysin activity.[3, 4] The treatment is repeated intravenous infusions of blood, plasma or 4 to 6 grams of fibrinogen (fraction I).

Certain fibrinolysins may be present to lyse the fibrin clot. This is one of the newest phases of coagulation which has not been completely and thoroughly studied.[2-4] There is a profibrinolysin (plasminogen) in serum and in Cohn's fraction III of the plasma. This is evidently an inactive precursor which is converted by an enzyme fibrinolysokynase into fibrinolysin (plasmin). This enzyme is in various tissues especially the lung and the uterus and in serum. There is also an inhibitor to this enzyme called antifibrinolysin. This balance system usually is carefully regulated and it is thought that this balance is kept in check by the pituitary-adrenal axis. Under conditions of stress such as shock or electroconvulsive therapy or other conditions previously mentioned under fibrinogen defects the inhibitors to fibrinolysin and the enzyme involved may disappear or decrease in amount which allows the fibrinolysin to become active and dissolve the fibrin clot.

SCREENING TESTS

The differential diagnosis from the laboratory standpoint in the diagnosis of bleeding will now be presented. (Table 3) The history is most important in determining whether bleeding is on a local basis or whether it is on a systemic basis. It is rare to have a generalized hemorrhagic disease

TABLE 3
DIAGNOSTIC PLAN OF ATTACK

1. History
2. Capillary fragility test
3. Complete blood count and smear
4. Ivy bleeding time
5. Lee-White coagulation time
6. Clot retraction or lysis
7. Prothrombin time (one stage)
8. Prothrombin consumption test

without previous history. The best screening tests which may and should be done will be the capillary fragility test, routine blood examination of which examination of the peripheral blood smear is most important, bleeding time (Ivy), coagulation time (Lee-White), clot retraction or lysis, one stage prothrombin time and the prothrombin consumption test.[2] More complicated tests are used to detect the defects which become apparent from the above tests.

LABORATORY PROFILE

We shall begin with certain vascular investigations and proceed to the investigation of the various defects in actual blood coagulation. (Table 4) These capillary fragility tests with which you all are familiar are positive in thrombocytopenic purpuras, in scurvy and in thrombasthenia. It also may be positive in hereditary telangiectasis (Rendu-Weber-Osler disease).

The platelet count is decreased naturally in thrombocytopenia from any cause.

Bleeding time is prolonged in thrombocytopenia, in the thrombasthenia, in very severe prothrombin deficiencies, in AC globulin or the labile factor deficiencies and in severe hemophilia. It is preferable to do the Ivy bleeding time which seems to properly control the various vascular factors which may not be properly evaluated in the bleeding time from the ear or finger as is usually done. In the Ivy bleeding time a tourniquet is placed around the arm and is inflated to just above the venous pressure and the stylet is then inserted to a depth of 1 mm. in the smooth surface of the forearm.

The coagulation time is characteristically prolonged in hemophilia although there are some cases of hemophilia that have a variable coagulation time and at certain times in this disease the coagulation may be entirely normal. The prolongation is not corrected by normal serum. PTC or component deficiency also will produce a long coagulation time which is corrected by normal serum. PTA deficiency recently described will produce slight change of the clotting time. Fibrinogen deficiencies, severe prothrombin deficiencies and circulating anticoagulants will also produce prolonged coagulation time. Convertin deficiencies or deficiency in the stable factor also may produce changes in the coagulation time.

Quick advocates the use of the recalcified coagulation time.[5] It is abnormal in hemophilia and in marked prothrombin deficiency. This recalcified coagulation time measures the coagulation of plasma centrifuged at high speed which removes the platelets. This plasma clots a great deal slower in hemophilia than that centrifuged at low speed because of increased resistance of platelets to disintegrate. Calcium is added to both. He feels that this is a definite test to be used in the diagnosis of hemophilia and shows that in some way platelets are related to hemophilia and thromboplastinogen. If plasma is platelet free, neither the addition of normal or hemophilic platelets will change the clotting time, but either type of platelet plus plasma are necessary.

The thromboplastin generation test is one of the most valuable of all of the recent tests for the diagnosis and the differential diagnosis of bleeding. This test allows each component of the first phase of blood coagulation (the thromboplastin producing system) to be measured separately and in doing this test adequate amounts of all except one factor are added to the unknown blood to be tested. Quick [5] describes another similar test which he calls the thromboplastin activity test. This is also thought to be valuable. These tests very clearly differentiate a plasma thromboplastic component deficiency from hemophilia.

The one stage prothrombin time done by the Quick method is very useful as a routine laboratory procedure because it

TABLE 4
LABORATORY PROFILE

Test	Disease
A. Capillary Fragility Test Positive	A. Thrombocytopenic purpuras Scurvy Hereditary telangiectasia Thrombasthenia
B. Platelets decreased	B. Thrombocytopenia
C. Bleeding time prolonged	C. Thrombocytopenia Thrombasthenia Severe hemophilia Severe prothrombin deficiencies Proaccelerin to accelerin defect (labile) (Parahemophilia)
D. Abnormal clot formation, retraction or lysis	D. Thrombocytopenia Thrombasthenia Fibrinogen deficiencies Fibrinolysin activity
E. Coagulation time prolonged	E. Hemophilia Component deficiency Antecedent deficiency Severe prothrombin deficiency Proconvertin to convertin defect (stable) Fibrinogen deficiency Circulating anticoagulants
F. Recalcified coagulation time abnormal	F. Hemophilia Severe prothrombin deficiency
G. Thromboplastin generation test	G. Differentiates phase I abnormalities: Platelet thromboplastic factor Plasma thromboplastic factor Plasma thromboplastic component Plasma thromboplastic entecedent
H. Prothrombin time prolonged One stage	H. Hypoprothrombinemia Proaccelerin to accelerin defect (labile) Proconvertin to convertin defect (stable) Fibrinogen defects Anticoagulants
I. Prothrombin time prolonged Two Stage	I. Hypoprothrombinemia
J. Prothrombin Consumption Poor	J. Thrombocytopenia Thrombasthenia Hemophilia Component deficiency Antecedent deficiency Proaccelerin to accelerin defect (labile) Circulating anticoagulants
K. Tests for anticoagulants	K. Hyperheparinemia Hemophilia-like anticoagulants
L. Specific tests for various factors	L. Plasma thromboplastic factor Plasma thromboplastic component Proaccelerin to accelerin defect (labile) Proconvertin to convertin (stable factor)

is simple and can be done by a laboratory that is well-equipped in a standardized form without much, if any, variation. The one stage method measures the speed of the reaction of an unknown specimen of oxalated blood as compared to normal oxalated blood. It measures the plasma clotting time (prothrombin time) after the addition of optimal amounts of calcium and thromboplastin. The time is the mini-

mal interval that elapses before a macroscopic fibrin clot results from the conversion of prothrombin to thrombin. Variables that are present are the velocity of the thrombin-fibrinogen interaction and the deposition of the insoluble fibrin gel and the competitive effect of antithrombin inactivating the thrombin. Owren's modification of Quick's original test is said to be the most reliable. The one stage method will be prolonged in hypoprothrombinemia, AC globulin deficiency, in conversion factor deficiency, in fibrinogen defects and in circulating anticoagulants. It must be emphasized that a normal one stage prothrombin time excludes significant fibrinogen defects. Calcium chloride, thromboplastin, and prothrombin-free plasma are added together to the unknown plasma and the speed of coagulation is then measured.

The two-stage method will differentiate clearly hypoprothrombinemia from the other factors which produce one-stage prothrombin prolongation. This measures amounts of prothrombin by measuring the amount of thrombin formed in unknown plasma when calcium and thromboplastin are added to the serum. The oxalated blood is first defibrinated with thrombin to get rid of the fibrin clot after the blood is allowed to clot (thus not using up any prothrombin). The prothrombin is converted into thrombin in the presence of adequate amounts of calcium and thromboplastin. Supplementary amounts of serum prothrombin conversion accelerator must be added if a deficiency exists. This amount of thrombin formed is measured by determining the highest dilution of defibrinated plasma which will produce clotting of the standard fibrinogen solution in a specified period of time which has been standardized against known amounts of thrombin. Thus the amounts of thrombin formed in the reaction will be measured.

The prothrombin consumption test is also a valuable test and it is probably second in value to the thromboplastin generation test. This test will show a poor prothrombin consumption in hemophillia, thrombocytopenias, circulating anticoagulants, in cases of component and antecedent deficiencies, as well as thrombasthenia and AC globulin deficiencies. It measures the amount of available thromboplastin. Normal blood is placed in several plain test tubes. The prothrombin time is determined before (in the plasma on an oxalated sample) and after coagulation. Most prothrombin disappears (probably by conversion to thrombin) in sixty minutes as measured in the serum after coagulation occurs. If less than 15 to 20 per cent is left, then it is normal. If more than 15 per cent is left, it demonstrates that the prothrombin consumption is less than normal. This occurs in the various conditions which have been listed. Thromboplastic activity time is a modification of the prothrombin consumption test as described by Quick,[5] and it may differentiate thrombocytopenia from hemophilia. This test is abnormally short in hemophilia and is normal in idiopathic thrombocytopenic purpura.

Clot retraction is a function of the platelets and it is poor in thrombocytopenia and thrombasthenia. In hypofibrinogenemia the clot is small, flabby and often extrudes red cells from its mass. In afibrinogenemia the clot does not form at all in the presence of thrombin. If excess fibrinolysin activity is present the clot may form but lysis or fragmentation occurs.

Tests for circulating anticoagulants are also important and it may help to differentiate hyperheparinemia from some other types of circulating anticoagulants. Minute amounts of blood or plasma will prolong the coagulation time of normal blood. There are two types of circulating anticoagulants. First the hyperheparinemia or heparin-like substance which is similar to a hypoprothrombinemia type of disease. It seems to interfere with the conversion of prothrombin to thrombin. Protamine titration tests permit a quantitative estimation of this material. The treatment for this is protamine or toluidine blue, both basic substances.

The hemophilia type of disease prevents the conversion of the plasma thrombo-

plastic factor (antihemophilic globulin) into thromboplastin. Anticoagulants of this type may be found in hemophiliacs after many transfusions. This anticoagulant is associated with the pseudoglobulin fraction of the plasma. Other patients with signs of iso-immunization may have this type of circulating anticoagulant and many recover spontaneously.

Antihemophiliac factor can now be measured by its corrective effect on the clotting defect of hemophiliac blood. Measurement of plasma thromboplastic component can be similarly assayed. However, both require the freshly shed blood from patients with their respective disease.

It is possible also to measure AC globulin or the labile factor in a special way. Since the labile factor disappears from aging plasma, it is assayed by its ability to correct the retarded prothrombin conversion (elevated prothrombin time) of stored oxalated human plasma. Values are expressed in terms of normal pooled plasma. The two stage method may be used.

The amounts of stable factor or convertin with special tests may be measured by its effect in lowering (returning to normal) the elevated prothrombin time of a plasma known to be deficient in this serum prothrombin conversion accelerator factor as found in patients with this abnormality or in bovine plasma specially treated to remove the stable factor.

Thus it is possible with the use of various tests, most of which are available in the ordinary commercial laboratory, to differentiate the various causes of abnormal bleeding.

SUMMARY AND CONCLUSIONS

Because this problem has become so complex, as we learn more and more about coagulation and bleeding it seems that we actually know less and less. Yet this is not true for in recent years by discovering new factors involved in blood coagulation we have discarded hitherto vague and uncertain classifications and replaced them with accurate diagnoses. How many have seen and diagnosed fibrinogenopenia as a postpartum or postoperative complication? Yet with newer accurate techniques we may specifically treat this condition with fibrinogen rather than relying on huge amounts of blood with their attendant dangers to correct the situation.

While this discussion may leave you somewhat at sea about many conditions, terms and laboratory tests, it must impress you with the fact that a few moments of carefully planned probing questions about previous bleeding and bruising history together with a profile of screening laboratory tests will save much grief, morbidity, and mortality.

REFERENCES

1. Ackroyd, J. F.: Allergic purpura, including purpura due to foods, drugs, and infections, Am. J. Med. 14:605, (May), 1953.

2. Alexander, Benjamin: Coagulation, hemorrhage and thrombosis, New Eng. J. Med. 252:432. (March 17), 1955; 252:484, (March 24), 1955; 252:526, (March 31), 1955.

3. Coon, W. W., Hodgson, P. E.: Fibrinolysis in surgery patients. I. Possible relation to a hemorrhagic diathesis, Surg., Gyn. & Obst. 95:717, (December), 1952.

4. Penn, S. R., Walker, J. H.: Defective blood coagulation following pulmonary surgery, New Eng. J. Med. 250:764, (May 6), 1954.

5. Quick, A. J.: Hemophilia, Am. J. Med. 14:349, (March), 1953.

6. Ratnoff, O. D., Pritchard, J. A., Colopy, J. E.: Hemorrhagic states during pregnancy, New Eng. J. Med. 253:63, (July 14), 1955; 253:97, (July 21), 1955.

7. Stefanini, Mario: Mechanism of blood coagulation in normal and pathologic conditions, Am. J. Med. 14:64, (January), 1953.

8. Sturgis, C. C.: Hematology, Second Ed. Springfield. Chas. C. Thomas, 1955.

9. Symposium: What is Hemophilia? Blood. 9:244, (March), 1954.

10. Wintrobe, M. M.: Clinical Hematology. Third Ed. Philadelphia, Lea & Febiger, 1951.

—o—

THE PROBLEM OF PANCREATITIS; SURGICAL ASPECTS *

WILLIAM R. SCHAFFARZICK, M. D.
BATON ROUGE

For many years pancreatitis was thought to be a relatively rare disease and the problem that it presented to surgeons was usually faced only at exploratory laparotomy. Recently, however, pancreatitis is being diagnosed frequently preoperatively and the incidence is considerable. Needless to say, the harder one looks for it, the more often it is found preoperatively.

* Presented at the Seventy-sixth Annual Meeting of the Louisiana State Medical Society, Alexandria, La., April 24, 1956.

In the evolution of thinking concerning this malady, many pathological terms have been applied and this has served mostly to confuse the clinician. Actually, there are many gradations as to acuteness and severity of the same disease process. Ordinarily now when we think of pancreatitis clinically, we are not speaking of the acute fulminating hemorrhagic pancreatitis which is seen at autopsy or at laparotomy when a mistaken diagnosis has been made. Rather we are thinking of a less severe, reversible inflammatory reaction in the pancreas.

PATHOGENESIS

The pathogenesis of the disease, in its early stages is seen only to show interstitial edema and inflammatory reaction of minor degree. This reaction may progress in an acute severe attack to rupture of the acini with thrombosis of the interstitial vessels and digestion of surrounding tissue by the activated enzyme of the gland with resulting hemorrhage and fat necrosis. Still later calcium is deposited in these areas of fat necrosis to produce soap. With repeated mild, acute attacks which never progress to the severity mentioned above, the edema subsides and interstitial fibrosis occurs. This may also be accompanied by formation of cyst-abscesses and pancreatic stones and result in eventual destruction of the gland because of scar. This end result is commonly seen in those patients who are diagnosed as having recurring acute pancreatitis.

From a surgical standpoint we are interested in classifying the disease in two ways so that some attempt at definitive treatment may be done. The so-called primary pancreatitis, therefore, is merely any gradient of inflammatory disease of the pancreas which is idiopathic in nature under our present concepts of the disease. On the other hand, secondary pancreatitis is usually thought of as an inflammatory reaction of the pancreas related to cholecystitis, common duct stones, duodenal diverticulae, metaplasia of the pancreatic ducts or spasm of the sphincter of Oddi. The methods of surgical therapy must, therefore, depend on the type of pancreatitis with which one is dealing.

ETIOLOGY

The etiology of pancreatitis is varied since the disease may be associated with other organic troubles. It is felt, however, that Opie's [1] theory of blockage of the ampulla by one means or another, the presence of a common channel between the bile ducts and pancreatic ducts, with reflux of bile into the pancreas as the inciting cause of the disease has long been over-emphasized. On the basis of autopsy studies, the presence of pancreatitis without associated biliary or ampullary disease, and the fact that injection studies of the pancreas with bile which resulted in pancreatitis are not valid since the pressures used were beyond physiological limit, one must concede that the common channel theory is not universally the underlying cause of the disease. In addition to this, it is now well understood that bile is not necessary to activate trypsin, thereby resulting in the picture of acute pancreatitis. It is known that trypsin can be activated by tissue fluids and it, of course, comes in contact with these fluids when acini rupture. Therefore, the theory propounded by Lium and Maddock,[2] that pancreatitis ensues when blockage of the pancreatic ducts either by mechanical means or as a result of spasm of the ampullary sphincter and/or pancreatic ducts themselves when the gland is actively secreting as following a heavy meal or ingestion of alcohol is a means of explaining most cases of pancreatitis. It is needless to say that there are a few other causes of pancreatitis which are less common as that seen following trauma to the pancreas, and a certain small incidence which is associated with infections such as the pancreatitis one sees occasionally with mumps.

On the basis then of the above philosophy, there are two classifications as to etiology of the disease.

SURGICAL TREATMENT

Our present concepts of definitive sur-

gical treatment are outlined as follows. Virtually all efforts have been directed toward correction by one means or another of the common channel. As indicated above, this situation does not exist in all cases. However, most efforts have been directed toward its correction whether present or not. Direct attacks along these lines include reimplantation of the pancreatic duct into the duodenum at a site away from the ampulla. As I see it, this is a very difficult method technically as the pancreatic duct is a small structure so that its isolation, division, and re-anastomosis into the duodenum require a most meticulous dissection which is accompanied with a considerable amount of trauma to the pancreas. Another direct method is the diversion of the common bile duct which too is an operation of considerable magnitude. The common duct must be divided and anastomosed either into the duodenum away from the ampulla, or better still into a defunctionalized loop of small bowel—the so-called Roux-Y loop—in an effort to prevent reflux of intestinal contents up the biliary tree. Indirect methods used in an effort to correct the common channel are operations of considerable less difficulty. Doubilet and Mulholland [3] have for several years championed various methods of division of the sphincter of Oddi either by use of a blind method through the common duct or a direct attack on the sphincter through the opened duodenum. As indicated above, this method is based on the assumption that the common channel exists and the spasm of the sphincter results in pancreatitis. These investigators have shown conclusively that spasm of the sphincter does occur after the injection of morphine or the presence of hydrochloric acid on the ampulla itself. They have had good results following this method of treatment. However, one cannot overcome the theoretic possibility of reflux of intestinal contents into the pancreatic and biliary tree once the sphincter is destroyed, resulting thereby in ascending cholangitis. It is certainly a point against this procedure on theoretic grounds as sphincter destruction in the dog always results in cholangitis if antibiotics are not given. Other investigators have employed the subtotal gastric resection as an indirect method of treatment of pancreatitis on the thesis that diversion of this kind prevents spasm of the ampullary sphincter, thereby stopping the resulting pancreatitis.

It goes without saying that the pancreatitis secondary to other diseases is treated by direct correction of the other primary disease. A distinct percentage of pancreatitis accompanies cholecystitis and cholelithiasis and hence cholecystectomy under these circumstances may be curative. Those patients with common duct stones, of course, are benefited by removal of these stones and drainage of the common bile duct and there are certain reported cases where drainage of the common duct itself resulted in improvement of pancreatitis even though no organic disease was present in the common bile duct. Pancreatitis accompanying peptic ulceration of the duodenum is fairly common and should be improved by proper treatment of the peptic ulcer either by medical management or properly applied surgical procedures. Obstruction of the ampulla or pancreatic ducts secondary to various tumors will result in pancreatitis, and if tumor is the inciting cause, then local excision or the Whipple operation will result in improvement of the pancreatitis.

As pancreatitis, either acute fulminating or acute recurrent, is accompanied by a large amount of abdominal and back pain, symptomatic treatment consists of splanchnic block and in those long standing cases, a splanchnicectomy. It must be pointed out, however, that this treatment merely stops the pain resulting from the disease. As we ordinarily consider acute recurrent pancreatitis a progressive disease, this treatment is considered purely symptomatic. Reports are in the literature of patients treated by splanchnicectomy with abolition of pain; however the disease

progresses unabated as shown by continued elevated serum amylases.

As discussed above concerning the etiology of pancreatitis, it was pointed out that a certain percentage of people suffering with acute recurrent pancreatitis have no accompanying organic disease that can explain the resulting inflammatory reaction of the pancreas. In general, it must be pointed out that these patients resemble the ulcer patient as concerns general habitus and emotional background. Careful history will reveal an unstable personality as manifested by inability to hold a job, difficulty in marital situations and actual psychosis. These people frequently are alcoholics and there is considerable doubt as to whether the alcoholism causes the pancreatitis or is merely a manifestation of their psychic troubles. Much research has been done along these lines as concerns the effect of the higher centers on the pancreas through the vagus nerves. In general, one may say that overstimulation through the vagus by higher centers results in an increased secretion of high enzyme content with an accompanying spasm of the ampulla and pancreatic ducts themselves. This then could be an ideal situation for the production of pancreatitis of either mild or severe degree if one believes the theory of Lium and Maddock concerning etiology. With this thought in mind a number of animal experiments were done which merely added to our interest and belief in this theory.[4] As a consequence a series of 14 cases have been done in which recurrent acute pancreatitis was treated by subdiaphragmatic vagotomy.[5] These patients have been followed from two to four years and in no instance has a bona fide attack of pancreatitis been observed postvagotomy. All these patients fitted into the situation as described above in that there was no obvious organic reason for their pancreatitis and careful psychological studies indicated an emotional imbalance Postoperatively they have been well and have returned to work. Several who were narcotic addicts are now cured of their addiction and in general we have been pleased with results. This method of treatment, however, we have found necessitates drainage of the stomach either by a dependent gastrojejunostomy accompanying vagotomy or a pyloroplasty since the vagotomy results in gastric retention in a high percentage of cases. Of this group of patients, one death occurred and this was due to an insulin reaction. He was our most severe case and had evidence of clinical pancreatic insufficiency. At autopsy no demonstrable pancreatic tissue could be found. It must be pointed out that the pancreas can function perfectly well without vagus innervation at a local reflex level and that this operation per se does not alter pancreatic function but merely protects it from the overstimulation from higher sources.

Pancreatitis itself results in certain complications and the surgical treatment of these complications consist of drainage of cyst-abscesses either externally or internally. However the internal method is the procedure of choice. This is usually accomplished by anastomosing the wall of the cyst to some adjacent hollow viscus but ideally is performed by diverting the cysts into a Roux-Y loop of jejunum. The external drainage, or the so-called marsupialization, usually results in a drainage lasting for years and is hence less desirable. Certain cysts complicating the pancreatitis can be excised completely and if so this is a satisfactory method of treatment. Late in the disease, stones are found in the pancreatic ducts and in some instances these stones can be removed; however; this procedure is accompanied by the danger of a pancreatic fistula and is not a procedure leading to a complete recovery. A few cases of far advanced pancreatitis with a chief complaint of pain have been treated by pancreatectomy. This procedure is exceedingly difficult from a technical standpoint as the gland is usually badly scarred and densely adherent to the adjacent large vessels. Several of these patients, however, have recovered from the surgery

and have lived a pain-free life with surprisingly small disability as a result of pancreatic insufficiency. In most hands, however, this operation is so difficult that it has little practical importance.

At the present time the philosophy concerning pancreatis is that the acute fulminating attack is best treated conservatively by means of gastric suction, antibiotics, parenteral fluids, and banthine. Any complications that arise from this acute attack must be treated as indicated above. Those patients, however, who have the so-called recurring acute pancreatitis in whom no associated organic disease can be found are best treated by the use of the psychogenic block accomplished by subdiaphragmatic vagotomy and gastrojejunostomy. It is felt that this will stop the progress of this disease which leads eventually to pancreatic insufficiency. More time must evolve before this statement can be proved.

REFERENCES

1. Opie, E. L.: The etiology of acute hemorrhagic pancreatitis, Bull. Johns Hopkins Hosp. 12:182, 1901.
2. Lium, R., and Maddock, S.: Etiology of acute pancreatitis, Surgery. 24:593, 1948.
3. Doubilet, H., and Mulholland, J.: Eight-year study of pancreatitis and sphincterotomy, J.A.M.A. 160:521, 1956.
4. Schaffarzick, W., Ferran, H., and McCleery, R.: A study of the effect of vagotomy on experimental pancreatitis, Surg. Gyn. Obst. 93:9, 1951.
5. Schaffarzick, W., Further clinical study of the effect of vagotomy on recurrent acute pancreatitis, Jour. Nat. Med. Assoc. 46:22, 1954.

PRINCIPLES IN THE REPAIR OF HERNIAS*

VINCENTE D'INGIANNI, M. D. †
NEW ORLEANS

Hernias will always be with us, it seems, because they are congenital, because they are a complication of surgery, and because some individuals develop hernias due to unknown pathogenesis.

As a consequence hernia repair is a popular subject for medical writing. Its popularity seldom wanes. The material being written on hernia repair is as voluminous in the present as it was in the past. The number of techniques which have been described is beyond calculation. Each surgeon believes he has found a technique that is satisfactory in his hand and he wishes to set it down as *the* method of repairing a given type of hernia.

ELASTICITY AND ADEQUACY OF TISSUES

After the skin has been opened in the repair of a hernia, the surgeon's first and foremost thoughts should be: Are the tissues elastic, is the freed tissue adequate in quantity? If so, then tissue approximation by any method will give good results. But this decision is often most difficult and the point of determination is uncertain. Frequently, one feels that the patient may heal satisfactorily without reinforcement, even when the tissues seem inadequate. However, when weak and insufficient tissues are placed in coaptation the result is increased fiber strain. Often a surgeon is influenced by the fact that this is the first repair. But he must remember that tissue of poor quality will not hold whether it is the first repair or a subsequent one. He must decide whether the strain and stress upon a given piece of tissue will exceed its elasticity. It is far safer to employ a substitute material in repairing a hernia than to take the risk of recurrence. Telling the patient that the next time the hernia recurs it will be necessary to employ a substitute material is a waste of time and dollars. The more recently recommended re-enforcing materials, fascia and tantalum mesh, show a relative sparcity of complications so that their use is encouraged.

CAPACITY FOR WOUND HEALING

Another point of importance in the repair of hernias is to know the relative value of tissues in regard to wound healing and the relative degree to which tissues are able to repair themselves. At the risk of sounding elementary we should remind ourselves that the surgeon does not repair tissues; he approximates tissues, and the body, by the process of wound healing, does the actual repair work. Suture material holds tissue together so that during the next ten to fifteen days the body is able to bring about the necessary repair. To

* Presented at the Seventy-sixth Annual Meeting of the Louisiana State Medical Society, Alexandria, La., April 25, 1956.

† From D'Ingianni Medical Foundation.

encourage wound healing one must use small calibre suture material and needle and must incorporate small quantities of tissue in the suture. Because the incorporated tissue is not viable any type of suture material may be used providing it holds sufficiently long for the healing or cementing process to be carried out to completion.

When we say that tissue is able to repair itself, we mean it can regenerate or fuse itself sufficiently to carry on the function as it did prior to its injury. This is only possible if the nerve supply is not incarcerated in suture material or divided. Nerve material will not regenerate, and without this important structure the physiology of the organ is markedly altered and proper healing is inhibited.

FIBROUS TISSUE

Fibrous tissue must also be given special attention in hernia repair. This tissue is best divided parallel to its fibers rather than transecting them, so as to reduce the stress and strain on the divided fiber when the patient stands, coughs, or bends. By dividing this tissue paralleling its fibers the point of stress is reduced to a minimum area. The transversalis fascia is to be constantly kept in mind as tissue that should be approximated regardless of its thickness. Frequently in approximating the peritoneum one neglects pulling together the thin layer of fibrous tissue. When it is fairly well developed it should be brought together in a separate layer of suturing rather than with the peritoneum. It has been said that the recurrence of hernias is in a large proportion due to the failure of approximating the transversalis fascia.

Since the blood supply in the abdominal area not only traverses in a longitudinal manner but also in a transverse manner with multiple anastomotic areas, it is hardly conceivable to devitalize these tissues. Yet blood supply to tissues is vital, so it is wise during hernia repair to save as many vessels as possible.

RESTORATION OF SAC CONTENTS

Good judgement is necessary in deciding how much space to leave where some normal structure of the body must traverse, such as: inguinal, femoral, and hiatal openings. If the space is closed too tightly that will cause strangulation of transmitted tissue. If there is more space than necessary this may promote recurrence of the hernia. It is of prime importance to restore the contents of the sac into the abdominal cavity. Frequently, we encounter large sacs that contain a great deal of abdominal content and it seems to be very difficult to replace the contents within the abdominal wall. This happens when we have not completely dissected the hernial ring which is causing the constriction. It is essential that this ring be adequately divided so that all of the hernial contents be restored to the abdomen with minimal trauma. Also, it is wise to search the omentum carefully for any bleeding that may result after an injudicious dividing of the omentum.

Case Report: Mr. C. W. The patient had a postoperative hernia through a midline incision which had been repaired the same morning. During the procedure the surgeon had found it difficult to slip the omentum into the abdominal cavity. Therefore, he quickly divided a piece of omentum, simplifying the procedure. That evening the patient went into profound shock. There was evidence of loss of blood. Upon exploration that night the patient was found to be actively bleeding from the divided omentum.

This case emphasises two points to be remembered in restoring the sac contents to the abdominal cavity: (1) there must be sharp delineation between various organs and tissues; (2) adequately opening of the hernial ring and careful ligation of all bleeding points are most necessary. It is important to remember bleeding points which appear insignificant at the time when the content is passed through the ring may become active once they have been dropped into the abdominal cavity, due of course to the release of the compression of the vascular system.

PERITONEAL INSUFFLATION

There is an infrequent type of hernia in which the entire abdominal cavity has passed through the hernia ring. The contents have been beneath the skin for such a length of time that the abdominal cavity itself seems to have diminished in size to the extent that it can no longer retain all

of the abdominal organs. Peritoneal insufflations have been advocated for this condition and they have met with considerable success. However, the following is a report of a complication that arose during insufflations:

Mrs. J. C. This patient had a large postoperative ventral hernia through which a full term pregnancy had passed as well as the majority of the intestinal tract. After the delivery the majority of the intestinal tract was palpated through the hernial opening. It was decided that the abdominal cavity should be insufflated preoperatively so as to assure the surgeon of a cavity sufficiently large to hold the hernia content. Therefore, intraperitoneal injections of air were administered.

A few hours after the insufflation the patient developed severe cramps, nausea and vomiting; hyperperistalsis was heard. There was roentgenological evidence of intestinal obstruction. This patient was immediately explored and intestinal obstruction was found, with no apparent cause however. The opening of the abdomen, no doubt, released the pressure causing the obstruction.

Whenever insufflations of the abdomen are done it is wise to observe these patients carefully for such a complication as has been described.

REINFORCING MATERIALS

The repair of a hernia is usually not a medical emergency. During the past twenty years in private practice I have repaired in excess of 400 cases; of these only 17 cases required an emergency procedure for incarceration of the bowel. Usually, hernia repair can be delayed until the patient is in excellent condition.

A properly prepared patient is a prime requisite to good healing and a smooth anesthesia, which are most necessary in hernia repair. A patient's constant straining is a detriment to suturing of friable and retracted tissues. The placement of supportive materials requires time and properly relaxed tissues.

In my own personal experience there were complications following the use of reinforcing materials, but in no instance was it necessary to remove any of these materials. Tantalum mesh was found to be the most effective of all the materials tried, not only as a reinforcing material but also as a substitute for peritoneal wall where there was not sufficient peritoneum to cover the defect.

Case Report: Miss E. B. This patient had a malignancy that involved the anterior abdominal wall. A portion of the wall had to be removed thus making closure of the wound impossible. Mesh was sutured to the edge of the peritoneum and the transversalis fascia, and the skin was then pulled over the mesh. This gave the patient a fairly well supported abdominal wall.

Hernia repair certainly warrants discussion and study, but rather than expound new techniques or methods of repair, perhaps the only general directive should be to emphasize the evaluation of the tissues. Whatever I have learned about the repair of hernias during the past twenty years can be compiled into the following brief statements: (1) The success of the repair depends primarily on the quality and quantity of tissue used in the repair. (2) Apposition of similar tissue is mandatory. (3) To use some form of reinforcement is often wiser than to trust that reinforcement is not necessary.

SUMMARY

Hernia repair demands a knowledge of anatomy, for the success of the repair depends on the restoration of a jumbled mass of tissues to their normal relationship. The surgeon must exercise extreme patience in restoring the hernial content, for in haste he might perforate the gut or divide tissues. He must use keen judgement in evaluating each case, especially in determining whether there is sufficient tissue present to withstand the strain of daily living. He must be ingenious enough to invent a method of closure on a moment's notice. He must be familiar with the use of reinforcing materials and know when to employ them. He must not optimistically rely on the healing processes of the body when in so doing he may risk recurrence of the hernia.

———o———

THE "THERAPEUTIC TRIAL" AS A DIAGNOSTIC CRITERION IN HYPERTHYROIDISM *

IRVING SINGER, M. D. †
NEW ORLEANS

It is generally accepted that the diagnosis of hyperthyroidism is a clinical one. Further, the diagnosis can be made with reasonable assurance on the basis of a thorough history and physical examination in some 75 to 90 per cent of cases.[1] The remaining 10 to 25 per cent of cases are atypical enough to require the addition of laboratory data to support the clinical suspicion. It is to be emphasized that the laboratory examinations only add to the composite clinical picture. In this group of "difficult" cases, as well as in the more obvious cases, it is the final clinical picture after prolonged observation that is diagnostic.

The BMR, I^{131} uptake, and protein-bound iodine determination are the tests in relatively common use today for the estimation of thyroid function. The latter two, even now, are often not readily available to the clinician. Each of these tests is subject to error—error in performance of the test and error in interpretation of results.[1,2] None of these procedures is infallible and none is diagnostic in itself. That they are of definite clinical usefulness is certain, but even when the results of all are at hand definite diagnosis will still be in doubt in a significant percentage of cases.

These cases defying diagnosis by the usual methods constitute a heterogeneous group and include the older patient with "masked" hyperthyroidism; the hyperthyroid individual sine goiter; the patient with hypermetabolism not thyroidal in origin, and others. It is in this group of patients that the therapeutic trial becomes of diagnostic importance. In addition, when the clinician is unable to obtain certain indicated laboratory data—viz, PBI and I^{131} uptake—the therapeutic trial may be resorted to.

In order for a therapeutic trial to yield valid diagnostic results in any illness, certain qualifications must be met:

1. The agent used for the trial must have a specific action or effect upon the particular disease under suspicion.
2. The agent used should have no discernible effect which could be confused with a therapeutic response in the absence of the disease under suspicion.
3. The specific action of the agent must be reflected in measurable objective criteria in order to assay results of the test.

Specific medical treatment is available in the case of hyperthyroidism. So far as is known, the medical agents used in the treatment of hyperthyroidism have no effect in euthyroid persons which could be confused with a therapeutic response. Objective yardsticks to measure the results of therapy are usually present. Therefore, the therapeutic trial can yield valid results and be of great diagnostic significance.

The factors to be considered then in carrying out a therapeutic trial for the diagnosis of hyperthyroidism are:

1. Choice of drug
2. Dosage and dosage schedule
3. Duration of the trial
4. Assessment of results

CHOICE OF DRUG

There are at present two types of drugs which are suitable for a therapeutic trial in hyperthyroidism. These are (1) iodide —usually used in the form of Lugol's solution and, (2) the antithyroid drugs—propylthiouracil and methimazole (tapazol) being the most commonly used.

Iodide is time-honored as an "ideal" agent for the therapeutic trial. Its advantage is rapidity of action, producing rapidly assessable results. The disadvantages of iodide, however, are many. These disadvantages can be related to the mode of action of iodide, which, it will be remembered, has three actions with regard to the hyperactive thyroid (Figure 1).

1. Iodide promotes the formation of thyroid hormone and its storage in the gland

* Presented at the Seventy-sixth Annual Meeting of the Louisiana State Medical Society, Alexandia, La., April 24, 1956.

† Instructor, Department of Medicine, Louisiana State University School of Medicine, New Orleans, Louisiana.

as colloid. This action will persist as long as the drug is administered.

2. Iodide inhibits thyroid stimulating hormone (TSH).

3. Iodide prevents the release of thyroid hormone from the gland.

The last two actions of iodide are responsible for the therapeutic effect in hyperthyroidism. These two effects of the drug do not persist as long as the drug is given (Figure 2). They produce a maximum effect within ten to fourteen days usually. Then, despite continued administration, there is "escape", or gradual tapering off of these two effects of iodide.

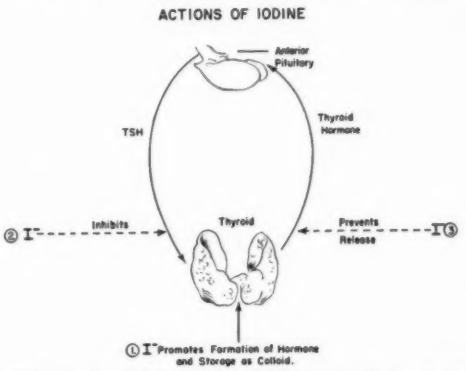

Figure 1.—Broken lines indicate actions 2 and 3 fail to persist even though administration of iodide is continued.

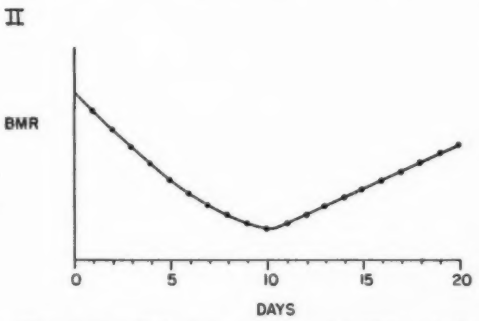

Figure 2.—Effect of continued iodide administration on one parameter of thyrotoxicosis. With continued administration there is gradual loss of effectiveness.

The disadvantages of I^- can now be enumerated: 1. The continued use of iodide is unsatisfactory for control of hyperthyroidism—the escape phenomenon referred to above.

2. Since the iodide treated gland is saturated with I^-, the results of I^{131} uptake studies, which may later be desired, will be invalid for a period of six weeks or more. For the same reason, the use of I^{131} for therapy becomes difficult or impossible for a like period of time. This is quite important as often the individual in whom the therapeutic trial is carried out is the ideal candidate for I^{131} therapy. We are then left in the position of having a diagnosis but being unable to carry out ideal therapy.

3. When one wishes to institute antithyroid drug therapy in a patient previously taking iodide, one must expect a delayed, slow response. The antithyroid drugs are effective in hyperthyroidism because they inhibit an enzyme system whose function is necessary for high rates of synthesis of thyroxine. However, the antithyroid drugs have no effect on preformed hormone which will be present in abundance in the gland previously treated with I^-. This preformed hormone will be released from the gland at its own rate perpetuating the hypermetabolic state, and the effects of the antithyroid drug will not become apparent until the store of preformed hormone is exhausted.

4. Another disadvantage of the use of iodide therapy for the therapeutic trial is related to the fact that I^- is our most rapidly acting therapeutic agent in thyrotoxicosis and therefore highly useful in the management of thyroid crisis. If a patient in crisis has recently been on prolonged iodide therapy, he will already have received maximal beneficial effects and will be in the "escape" stage. Our therapeutic "ace-in-the-hole" will already have been played and no longer available for use when most needed.

For these reasons, it is my opinion that the use of Lugol's solution or other forms of iodide for the therapeutic trial should be abandoned in favor of the antithyroid drugs. The only advantage of iodide is the more rapid response obtained.

The antithyroid drugs, on the other hand, are eminently suited for the therapeutic trial. Their action, insofar as is known, is specific. That is, with adequate dosage correctly prescribed, a clinical response will occur in any hyperthyroid individual. There is no evidence of any such thing as refractoriness to antithyroid drug therapy. On the basis of present evidence, a response to antithyroid drug therapy indicates a diagnosis of hyperthyroidism—failure to respond indicates a euthyriod state. The euthyroid individual will have no discernable effect from antithyroid drugs in the usual dosages given. There is little to choose from between propylthiouracil and tapazol although the author personally prefers the latter. The *indiscriminate* use of antithyroid drugs should be avoided in view of the occurrence of agranulocytosis in a few individuals (less than 0.5 per cent) receiving these agents. However, the use of these drugs in discriminately chosen cases is well justified clinically by their effectiveness and the relative rarity of serious side effects.

DOSAGE AND DOSAGE SCHEDULE

Adequate dosage is obviously necessary. Propylthiouracil is usually recommended in dosages of 300 to 600 mgm. daily. For purposes of a therapeutic trial the lower value is probably too low. Four hundred and fifty to 800 mgm. daily is recommended for this purpose. The range of tapazol dosage is 30 to 80 mgm. daily. Forty milligrams daily is recommended for the therapeutic trial. In the event of equivocal results either drug can be increased to the maximum values given. In general, patients with a small diffuse goiter respond to smaller doses and the large nodular goiter requires higher dosage levels.

Correct timing of dosage is most important. These compounds are rapidly excreted and are not cumulative. They must be given in divided doses at no longer than six to eight hour intervals. To avoid misunderstanding, it is preferable to prescribe each dose at a definite time of day, e.g. tapazol mg. 10, one tablet at 6 a.m., noon, 6 p.m. and midnight.

DURATION OF THE TRIAL

How long should the trial be carried out? The usual patient with a diffuse goiter or no goiter and no previous iodide treatment will show a definite response within ten to twelve days and will be approaching the euthyroid state by twenty-one days. Therefore, a trial period of four to six weeks would seem adequate. The nodular goiter may require larger doses and a longer period of time to respond—but certainly some objective response may be expected within thirty to sixty days and often is seen earlier with adequate dosage. A total trial of eight to twelve weeks should yield satisfactory results in even the most stubborn case of nodular toxic goiter. The patient previously treated with iodides may take as long as three to six months to respond to antithyroid drug therapy depending upon the amount of stored hormone present.

The necessity for full cooperation of the patient seems too obvious to even mention, but occasionally must be assessed as a factor in evaluating results of the trial.

ASSESSMENT OF RESULTS

The evaluation of results of the trial is not usually difficult. The important point is that the response must be an objective one—the criteria necessarily varying from patient to patient dependnig upon the presenting signs and symptoms. Criteria such as pulse rate, body weight, tremor, quadriceps weakness, eye signs, and signs of peripheral vasodilatation, such as the hot moist palms and skin are useful criteria for evaluation. The response of previously refractory heart failure or the conversion of a cardiac arrythmia to normal sinus rhythm may be a guidepost. The BMR may on occasion be extremely useful as a criterion of response in patients who present few or none of the readily evaluated signs of thyrotoxicosis. The objective evaluation of the response to the therapeutic trial is the key to the usefulness of the procedure.

SUMMARY

In suspected cases of thyrotoxicosis the therapeutic trial is indicated when a thorough history and physical examination,

available laboratory data, and a reasonable period of observation do not solve the diagnostic dilemma. The antithyroid drugs are the agents of choice for the trial. The details of administration of the drugs are important for the trial to yield valid results. The results of the trial must be judged on the basis of objective criteria.

REFERENCES

1. Bauer, R. E.: The present status of the diagnosis of hyperthyroidism, Ann. Int. Med. 44:207, 1956.

2. Beierwaltes, W. H.: The value of the radioactive iodine uptake and protein bound estimation in the diagnosis of thyrotoxicosis, Ann. Int. Med. 44:40, 1956.

The Journal of the Louisiana State Medical Society

Established 1844

Published by The Journal of the Louisiana State Medical Society, Inc. under the jurisdiction of the following named Journal Committee:

Paul D. Abramson, M. D., Ex-Officio
E. L. Leckert, M. D., Chairman
C. M. Horton, M. D., Vice-Chairman
Sam Hobson, M. D., Secretary
Edwin H. Lawson, M. D.
J. E. Knighton, M. D.

EDITORIAL STAFF

Philip H. Jones, M. D.....*Editor*

COLLABORATORS—COUNCILORS

C. J. Brown, M. D.
J. E. Clayton, M. D.
Guy R. Jones, M. D.
Ralph H. Riggs, M. D.
C. Prentice Gray, Jr., M. D.
Arthur D. Long, M. D.
J. Y. Garber, M. D.
R. E. C. Miller, M. D.

C. Grenes Cole, M. D.....*General Manager*
1430 Tulane Avenue

SUBSCRIPTION TERMS: $4.00 per year in advance, postage paid, for the United States; $4.50 per year for all foreign countries belonging to the Postal Union.

News material for publication should be received not later than the eighteenth of the month preceding publication. Orders for reprints must be sent in duplicate when returning galley proof.

Manuscripts should be addressed to the Editor, 1430 Tulane Ave., New Orleans, La.

The Journal *does not hold itself responsible for statements made by any contributor.*

THE STATUS OF ANTIDIABETIC SULFONAMIDE COMPOUNDS

The antidiabetic detection drive of the National Diabetes Association will take place on November 11 through 17. Physicians cooperating in this drive, of whom it is hoped there are many, will have occasion to answer questions in formal addresses, and in informal remarks in regard to the present status of orally given antidiabetic sulfonamide compounds.

In the last three years in Germany, and more recently in this country, investigation of the use of these compounds has produced encouraging results. Unfortunately, it has resulted in widespread publicity in the lay press. Diabetics, and relatives who are concerned with the care of diabetics, are anxious to use the oral medications about which they have read glowing accounts. They feel that it will relieve them of the necessity of the use of insulin, and free them of many restrictions.

It is well, therefore, that the physician be adequately informed as to the status of these preparations. In this manner, physicians may build up a cautious attitude among patients who are diabetics, and get their cooperation in waiting for adequate scientific data and the accumulation of sufficient clinical experience before demanding their use. The individual diabetic has far too much at stake to exchange the trustworthy diabetic regime in general use at present for one whose complexities are yet to be determined.

The information at hand in regard to these sulfonamide compounds gives some promise of their being of considerable help to certain groups of diabetics.

The compound carbutamide (1-butyl-3-sulfanilylurea, designated substance BZ-55 by the German investigators, and known also in Germany as nadisan and invenol) has been shown to lower the blood sugar level. Another sulfonamide compound (1-butlyl-3*p*-tolylsulfonylurea), designated as tolbutamide, has also been shown to have this effect. Lowering of the blood sugar has been shown in normal animals and in human beings who are diabetic and nondiabetic. Carbutamide was first investigated for its antibacterial action in February 1954, by Franke and Fuchs.[1] Trying the preparation on themselves, they noted fatigue, perspiration, hunger, trembling, and a certain degree of euphoria. Blood sugar determinations showed a definite hypoglycemie effect. Extensive clinical trials followed these observations. It is quickly absorbed, and more slowly excreted. Within two or three hours after the ingestion of 2.5 grams, a definite lowering in the blood sugar level will occur. The

mode of its action has not yet been completely established. For this hypoglycemic action to take place, it seems necessary that there should be a sufficient number of the islets of Langerhans to produce a certain amount of insulin, or the presence of exogenously introduced insulin. The blood sugar level lowering effect can be obtained in the absence of the adrenals or pituitary, but in totally depancreatinized animals the effect on blood sugar is not significant.

Ferner and Runge[2] feel that the effect is on the alpha cells of the islands of Langerhans. Mirsky found carbutamide to be an inhibitor of insulinase, an enzyme which terminates the activity of insulin. By this hypothesis, carbutamide prevents the destruction of insulin by enzymic activity.

The toxicity of carbutamide is low. Occasional drug fever and drug eruption have been reported. Mental cloudiness has occurred in one patient. Occasional depression of the white blood cell count has been reported. Evidence also exists that potentiation of barbiturate action may occur. It has been remarked that the time of observation is too short to permit conclusions about the ultimate frequency of side effects from toxic reactions.

Clinical observations have indicated that the patients who respond favorably to the drug fall, in general, into the group of those who become diabetic in maturity, are obese, overweight, and have not required an excessive dose of insulin. Numerous European investigators have cautioned that its effects are not satisfactory in the juvenile diabetic, or those below 40, or in the thin, asthenic type, who have required large doses of insulin more than five years, and those whose sugar metabolism is unstable. It is not suitable for emergency treatment of a diabetic with acidosis, or those undergoing surgery, or for children.

The usual procedure has been to give the patient 2.5 grams the first day, 1.5 grams the second day, and 1 gram daily thereafter. Some authors have reported stopping the use of the drug after ten to fourteen days without the necessity of having to return to it over a matter of weeks and months. The majority, however, advise that the patient be kept on a maintenance dose of 0.5 to 1 gram a day. All observers express caution as to the care of the patient in emergency situations which deviate from his careful diabetic regime. The necessity for further proper adherence to the diabetic diet is as urgent as in our present established routine methods.

The grouping of individuals who respond and who do not respond to carbutamide has prompted certain authors[3] to classify diabetes. They feel that there are two types of diabetes, spoken of as insulin deficiency diabetes and counter-regulation diabetes. Carbutamide is frequently successful in controlling the latter and fails in the insulin deficiency type. Those diabetics of long standing with a tendency towards asthenic type who do not respond to carbutamide treatment, these authors believe, have in the course of years experienced a transformation of counter-regulation diabetes into an insulin deficiency diabetes. Lawrence[4] has previously divided diabetes into (1) lipoplethoric, (2) insulin deficient, and (3) lipo-atrophic (very rare).

The indications are, therefore, that this drug or one of similar type will become a useful aid to treatment of diabetes, but its proper usefulness, its hazards, and the limitations of its benefits have yet to be determined. In the forseeable future, even when its use is undertaken on an investigative basis, the transition from the diabetic state to its routine administration, or from insulin regime to its use, should be a hospital procedure.

REFERENCES

1. Ridolfo, Anthony S. and Kirtley, Wm. R.: Clinical experiences with carbutamide, an orally given hypoglycemic agent, J.A.M.A. 160:1285 (April 14) 1956.
2. Ferner, H. and Runge, W.: The Langerhans islands of diabetes after treatment with the oral antidiabetic BZ 55, Deutsche med. Wochensch. 81:331 (March 9) 1956.
3. Bertram, Ferdinand, Bendfeldt, Elinor, and Otto, Hellmut: Indications for and results of the peroral treatment of diabetes mellitus with a sulfonyl urea derivative; report on 335 cases, Deutsche med. Wochensch. 81:274 (Feb. 24) 1956.
4. Lawrence, R. D.: Three types of human diabetes, Ann. Int. Med. 43:1199 (December) 1955.
5. Editorial: Orally given antidiabetic sulfonamide compounds, J.A.M.A. 160:1320, (April 14) 1956.

DIABETIC DETECTION WEEK

The National Diabetes Association will have their annual Diabetes Detection Week between November 11th and 17th, 1956. The Louisiana Diabetes Association is requesting the cooperation of all physicians in this worthy endeavor to discover hidden diabetics.

Statistical surveys continue to indicate that there are as many diabetics unknown to themselves, and their physicians, as there are diabetics under treatment. If each physician's office is a diabetic detection center during the third week in November, many patients will benefit by having their condition understood.

The activities of the Diabetic Association are entirely those of physicians and they deserve our enthusiastic support.

ORGANIZATION SECTION

The Executive Committee dedicates this section to the members of the Louisiana State Medical Society, feeling that a proper discussion of salient issues will contribute to the understanding and fortification of our Society.

An informed profession should be a wise one.

AMERICAN MEDICAL ASSOCIATION CLINICAL MEETING

Seattle, Washington

November 27-30th, 1956

Are you making plans now to attend the A.M.A. Clinical Session in Seattle, November 27-30?

Various committees are working hard in preparation for the meeting and you can be assured that an outstanding scientific program and excellent hotel accommodations await those who attend this year's meeting.

In cooperation with the Council on Scientific Assembly, the general committee headed by Chairman M. Shelby Jared of Seattle has been working diligently for months and reports that plans are near completion.

The center of activities will be Seattle's Civic Auditorium, where scientific sessions will be held and exhibits will be displayed. Conveniently located the auditorium is easily accessible from downtown hotels, and transportation will be available for commuting to and from the meetings. A cafeteria will be operated in the auditorium for midday meals.

Clinical Session headquarters will be the Olympic Hotel, where House of Delegates sessions and meetings of the Board of Trustees, councils and reference committees will be held.

The scientific program will be beamed at the general practitioner, and subjects have been carefully chosen to be of interest and practical value. The program will include panel discussions, individual papers, motion pictures and closed-circuit television clinics.

The panel discussions will cover such subjects as hypertension, hemolytic anemia, prenatal care, problems of aging, epilepsy, low back pain, liver disease and vascular disorders. Twenty topics will be considered by panels of men prominent on the national scene and in the Northwest.

There will be 45 papers dealing with such subjects as fluid balance, urological problems, office psychiatry, varicose veins, fractures, diabetes and heart disease. Well-known medical educators and practicing physicians from all parts of the country will participate.

The television clinics will include both wet (operative) and dry (non-operative) programs. Talent will be drawn largely from Seattle because of the necessity of rehearsals and frequent briefing. There will be clinics on block anesthesia, treatment of burns, bleeding problems, intestinal obstruction, caesarean section, hand surgery, vein stripping and other subjects.

The program for the medical motion pictures and the schedule of papers, panels and television shows will be published soon in the A.M.A. Journal.

Scientific and technical exhibits have been arranged through A.M.A. headquarters. They promise to be as interesting and varied as in the past.

Elaborate plans are being made for a banquet and entertainment for the House of Delegates, Board of Trustees, A.M.A. officials and their wives on Wednesday evening, November 28th, in the headquarters hotel.

Prepaid medical service plans of Washington, Oregon and Idaho are planning to conduct a hospitality suite in grand style for three days during the session. The prepaid plans of these states also will present an exhibit of their services to the public.

Plans are near completion for Auxiliary activities during the Clinical Session. Sight-seeing tours and other events are on the agenda.

Physicians are urged to make their reservations early. A reservation form is appearing now in the A.M.A. Journal.

For your information, following are the Railroad Schedules:

Missouri Pacific Railroad Company

		Schedule		Example
Lv	New Orleans	Mo. Pac No. 3	8:35 AM	Sunday
Ar	Houston		6:10 PM	"
Lv	Houston	Santa Fe 66	6:45 PM	"
Ar	San Francisco	Santa Fe 1	1:30 PM	Tuesday
Lv	San Francisco	Sou Pac 12	4:00 PM	"
Ar	Seattle		1:00 PM	Wednesday
Return:				
Lv	Seattle	Sou Pac 11	12:30 PM	Sunday
Ar	San Francisco		9:15 AM	Monday
Lv	San Francisco	Santa Fe 2	11:00 AM	"
Ar	Houston	Santa Fe 65	8:15 AM	Wednesday
Lv	Houston	Mo. Pac 4	9:05 AM	"
Ar	New Orleans		7:15 PM	"

Fares

	Fare	Tax	Total
Round-trip first-class	$146.65	$14.67	$161.32
Pullman—each way.			
Lower berth	27.15	2.72	29.87
Bedroom—2 persons	59.70	5.97	65.67
Compartment—2 persons	65.15	6.52	71.67

Southern Pacific Lines

		Schedule		Example
Lv	New Orleans	Sunset Limited No. 1	10:45 PM, CT	Monday
Ar	Los Angeles		4:15 PM, PST	Wednesday
Lv	Los Angeles	The Owl No. 57	6:05 PM, PST	"
Ar	Oakland Pier		7:15 AM, PST	Thursday
Lv	Oakland Pier	Shasta No. 10	7:55 AM, PST	"
Ar	Portland		11:30 PM	"
Lv	Portland	Shasta No. 10	11:45 PM	"
Ar	Seattle		6:15 AM	Friday

This is streamline train from Oakland to Portland with chair car seats, and parlor car seats, change to pullman in Portland.

or

Lv	Los Angeles	The Lark No. 75	8:00 PM, PST	Wednesday
Ar	San Francisco		7:30 AM, PST	Thursday
Lv	San Francisco	Cascade No. 12	4:00 PM	"
Ar	Seattle		1:00 PM	Friday

This is also streamline train with through pullman from Oakland to Seattle.

———o———

MEDICAL NEWS SECTION

CALENDAR

PARISH AND DISTRICT MEDICAL SOCIETY MEETINGS

Society	Date	Place
Calcasieu	Fourth Tuesday every other month	Lake Charles
East Baton Rouge	Second Tuesday of every month	Baton Rouge
Morehouse	Third Thursday of every month	Bastrop
Natchitoches	Second Tuesday of every month	
Orleans	Second Monday of every month	New Orleans
Ouachita	First Thursday of every month	Monroe
Rapides	First Monday of every month	Alexandria
Sabine	First Wednesday of every month	
Tangipahoa	Second and fourth Thursdays of every month	Independence
Second District	Third Thursday of every month	
Shreveport	First Tuesday of every month	Shreveport
Vernon	First Thursday of every month	

SURGICAL ASSOCIATION OF LOUISIANA

The 9th Annual Meeting will be held on Sunday, November 4, 1956, at the St. Charles Hotel, New Orleans, La.

LOUISIANA ACADEMY WILL CELEBRATE TENTH ANNIVERSARY

The finest scientific program and entertainment has been made available to those attending the Tenth Annual Scientific Assembly of the Louisiana Academy of General Practice at the Jung Hotel in New Orleans, La. Oct. 9, 10, 11, 1956.

The scientific session will feature Dr. Malcolm Phelps, President-elect of the American Academy of General Practice; Dr. Philip Thorek, Clinical Associate Professor of Surgery, University of Illinois, College of Medicine; Dr. Robert Ross, Professor and Head of Department, Obstetrics and Gynecology, University of North Carolina School of Medicine, Dr. Wm. Paul, Professor of Medicine and Rehabilitation, Medical Director of Poliomyelitis and Rehabilitation Unit, Medical Director of Varsity Athletics, University of Iowa and Dr. Richard Kern, Professor of Medicine, Temple University, Philadelphia; Dr. Lawrence O'Neil, Surgeon in Chief, Independent Unit, Charity Hospital, New Orleans and Dr. T. A. Watters, Clinical Professor of Psychiatry at Louisiana State Medical School.

The program fulfills the requirements for the allowance of ten hours category I credit postgraduate education.

GASTROENTEROLOGICAL CONVENTION

The Annual Convention of the American College of Gastroenterology will be held at The Roosevelt in New York City on October 15, 16, 17, 1956.

The program this year will feature six panel discussions on the diseases of the gastrointestinal tract, one to be presented by each of the six medical schools in New York City. In addition, there will be individual papers and a special motion picture program.

There will be scientific, as well as commercial exhibits, and the sessions will be open to all physicians without charge.

Following the Convention, the Annual Course in Postgraduate Gastroenterology, under the personal direction of Dr. Owen H. Wangensteen of Minneapolis, Minn., and Dr. I. Snapper of Brooklyn, N. Y., will take place on October 18, 19, 20 1956, at The Roosevelt and the new Metropolitan Hospital Center. The faculty for the Course has been chosen from the medical schools in New York and adjacent areas.

The Postgraduate Course will be open only to those who have registered in advance.

Copies of the program and further information concerning the Postgraduate Course may be obtained by writing to: American College of Gastroenterology, 33 West 60th Street, New York 23, N. Y.

ACADEMIC DEDICATION

The University of Mississippi School of Medicine

October 23 - 24, 1956

Jackson, Miss.

PROGRAM

Tuesday, October 23

9:00 a.m. — Welcome, D. S. Pankratz, M. D., Dean of the School of Medicine and Director of the University Medical Center.

9:15 a.m. — "The Problems of Intersexuality." Bayard Carter, M. D., Professor and chairman, Department of Obstetrics-Gynecology, Duke University.

10:00 a.m. — "Psychiatry and Undergraduate Medical Education,"
G. N. Raines, (Captain M.C., USN) Head of Neuropsychiatric Branch, Professional Division, Bureau of Medicine and Surgery, Department of the Navy; Professor and Director of the Department of Psychiatry, Georgetown University.

11:00 a.m. — "Certain Unsolved Problems in Amebiasis."
Henry E. Meleney, M. D., Research Professor of Medicine, Louisiana State University.

12:00 noon — Tour of the University Medical Center

2:30 p.m. — "Nutrition and Atherosclerosis"
Frederick J. Stare, M.D., Professor and Chairman, Department of Nutrition, Harvard School of Public Health.

3:20 p.m. — "The Place of Pathology in Medicine of the Future."
Douglas H. Sprunt, M. D., Director of the Institute of Pathology, University of Tennessee.

4:20 p.m. — "Some Interesting Pediatric Diagnostic Problems."
Amos U. Christie, M. D., Professor and Chairman, Department of Pediatrics, Vanderbilt University.

7:00 p.m. — Dinner, Heidelberg Hotel
Alton C. Bryant, Provost, The University of Mississippi, Presiding.
Joseph C. Hinsey, Ph.D., Director of New York Hospital-Cornell Medical Center, Speaker. Topic to be announced.

Wednesday, October 24

9:00 a.m. — "X-Ray Screen Intensification and Its Import in Clinical and Experimental Medicine."
Russell H. Morgan, M.D., Professor and Chairman of Roentgenology, Johns Hopkins University.

9:50 a.m. — "The Contribution of Pyramidal and Extrapyramidal System to the Use of Skeletal Muscle in the Primate."
Marion Hines, Ph.D., Professor of Experimental Anatomy, Emory University.

10:50 a.m. — "Topic to be announced."
I. S. Ravdin, M. D., John Rhea Barton Professor of Surgery, University of Pennsylvania.

12:00 noon — Tour of the University Medical Center.

2:20 p. m. — "Basic Physiology as a Clinical Science."
Carl J. Wiggers, M. D., Cleveland, (Ohio) Clinic, Emeritus Professor of Physiology.

3:20 p.m. — "An Experimental Study of Combined Viral and Bacterial Infections."
G. John Buddingh, M. D., Professor and Chairman of Microbiology, Louisiana State University.

4:15 p.m. — "The Challenge of Mood-Altering Drugs."
C. D. Leake, Ph.D., Associate Dean, School of Medicine, Ohio State University.

(Approved for Credit, 10 hours Category 1, American Academy of General Practice)

WOMAN'S AUXILIARY TO THE LOUISIANA STATE MEDICAL SOCIETY

AUXILIARY VOLUNTEER IN MENTAL HOSPITALS

Mrs. W. A. K. Seale, President

The goal of any type of psychiatric activity is the eventual resocialization of the individual. In addition to services provided by professionals and hospital organizations it is proper and indeed necessary that society itself plays a part in rehabilitation procedures.

The patients in the mental hospitals are members of our families, our friends and our neighbors. Many of them have great ability and as wide a variety of interests and talents as any large group. Creative and constructive activities to fill the patients' free time, supplemented by visits and gifts which represent community respect and good will, are contributions that can be supplied only by volunteers since it is necessary for the employed staff to maintain a different relationship in order to attend to all their duties within a specified time.

Not all of you could work as volunteers in the hospitals even if you so desired. Since you would be working directly with the patients, it would be necessary that you be screened to determine your suitability for a particular type of work. Orientation of all staff employees and volunteers is of utmost importance and all volunteer activities are under the supervision of the director of volunteers and the employed staff.

Plan a program on mental health for your group or a tour of a hospital. The Central Louisiana State Hospital prints a folder entitled, "What You Can Do", in which the volunteer

services are listed in order of importance as follows: Visiting, Leadership, Give a Party, Rides and You—you can also help by getting your friends and neighbors interested. Listed in another section are the "Gifts That Are Needed", these are: Clothes, books, games, musical instruments, records, sheet music, radios, televisions, phonographs, scraps for rugs, fruits, cakes, candies (by the dozen or by the truck load) and cash gifts for parties and entertainment of patients.

It is difficult to conceive of any time in the near future when the work of volunteer groups will not be of value. There will always be hospitals and patients in those hospitals who need the extra measure of personalized attention which means so much to living human beings.

The talk by our President, Mrs. W. A. K. Seale, at the National AMA Conference in Chicago serves to remind us of the great need for volunteers in the field of Mental Health. As Auxiliary members we are needed to lead the way in this endeavor, but my appeal is directed to all doctors' wives to contribute to the success of this program. Each of us has something of great value to offer others. If in your own quiet way you knew that YOU were supplementing the inadequacy of others, wouldn't your mental picture be brighter? Offer your services NOW by contacting your local Auxiliary Mental Health chairman. Remember that whatever you give always returns threefold.

Mrs. Pierre A. Donaldson, Chairman
Mental Health, Woman's Auxiliary
to the La. State Medical Society.

Submitted by:
Mildred G. Carter, Chairman
Press and Publicity

—o—

BOOK REVIEWS

Normal Labor; by Leroy A. Calkins, M. D., Springfield, Illinois, Charles C Thomas, 1955, pp. 128, Price $4.00.

In this monograph the author discusses the physiology and management of labor and the puerperium, in the first fifty-three pages, and then devotes sixty-seven pages to the reprinting of seven papers previously published by him dealing with various phases of labor, and setting forth his views thereon. It is interesting to note that in the first section he deals chiefly with the physiologic and anatomic changes that occur in labor, and with the general management of labor and the puerperium. He gives no directions as to the actual delivery of the baby, apparently feeling that the reader is fully conversant with that subject. He does set forth the details of the conduct of the third stage, laying great stress on its proper management in order to minimize blood loss.

In the second, or "appendix", section are found elaborations of topics discussed more or less briefly in the first part of the book. He has devoted much time to the study of the cervix in labor, the characteristics of "good", "fair", and "poor" pains, and the mechanisms of descent and rotation. The various points upon which he lays stress are familiar to every practicing obstetrician, but are not elucidated in most text books as clearly as they should be.

The author has developed a method of estimating the duration of labor in a given case, based on a study of the condition of the cervix, the character of the labor pains, and the station of the head in the pelvis. According to his reports, it works very well. Time will tell whether others will achieve the same success when applying the method according to the author's directions.

E. L. KING, M. D.

PUBLICATIONS RECEIVED

Grune & Stratton, Inc., N. Y.: The Labyrinth; Physiology and Functional Tests, by Joseph J. Fischer, M. D.; Studies in Topectomy, edited by Nolan D. C. Lewis, M. D., Carney Landis, Ph.D., and H. E. King, Ph.D.; Venous Return, by Gerhard A. Brecher, M. D.; Psychopathy and Delinquency, by William McCord, Ph.D., and John McCord, Ed. M.

Little, Brown & Co., Boston: Ciba Foundation Colloquia on Ageing, Volume 2, and Ciba Foundation Colloquia on Endocrinology, Volume IX, by various participants.

The C. V. Mosby Company, St. Louis: Clinical Urology for General Practice, by Justin J. Cordonnier, M. D.; J.A.M.A. Queries and Minor Notes, published for the American Medical Association; New Bases of Electrocardiography, by Demetrio Sodi-Pallares, M. D., with the collaboration of Royall M. Calder, M. D.

Philosophical Library, Inc., N. Y.: Sleep, the Way to Sound and Healthful Slumber, by Dr. Marie Stopes.

Henry Regnery Company, Chicago: Observations on Krebiozen in the Management of Cancer, by A. C. Ivy, M. D., John F. Pick, M. D., and W. F. P. Phillips, M. D.